(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 April 2004 (29.04.2004)

PCT

(10) International Publication Number
WO 2004/035746 A2

(51) International Patent Classification[7]: C12N

(21) International Application Number: PCT/US2003/032805

(22) International Filing Date: 16 October 2003 (16.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/419,432 17 October 2002 (17.10.2002) US

(71) Applicant *(for all designated States except US)*: **DECODE GENETICS EHF.** [IS/IS]; Sturlugotu 8, IS-101 Reykjavik (IS).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HELGADOTTIR, Anna** [IS/IS]; Hamravik 86, IS-112 Reykjavik (IS). **GULCHER, Jeffrey, R.** [US/US]; 130 South Canal Street, #9M, Chicago, IL 60606 (US). **MANOLESCU, Andrei** [RO/IS]; Eskihlid 22a, IS-105 Reykjavik (IS).

(74) Agents: **CARROLL, Alice, O.** et al.; Hamilton, Brook, Smith & Reynolds, P.C., 530 Virginia Road, P.O. Box 9133, Concord, MA 01742-9133 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUSCEPTIBILITY GENE FOR MYOCARDIAL INFARCTION

(57) Abstract: Linkage of Myocardial Infarction (MI) and a locus on chromosome 13q12 is disclosed. In particular, the FLAP gene within this locus is shown by association analysis to be a susceptibility gene for MI. Pathway targeting for drug delivery and diagnosis applications in identifying those have MI or at risk of developing MI, in particular are described.

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SUSCEPTIBILITY GENE FOR MYOCARDIAL INFARCTION

RELATED APPLICATION

This application claims the benefit of 60/419,432, filed October 17, 2002. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Myocardial infarction (MI) is one of the most common diagnoses in hospitalized patients in industrialized countries. Myocardial Infarction generally occurs when there is an abrupt decrease in coronary blood flow following a thrombotic occlusion of a coronary artery previously narrowed by atherosclerosis. Infarction occurs when a coronary artery thrombus develops rapidly at a site a vascular injury, which is produced or facilitated by factors such as cigarette smoking, hypertension and lipid accumulation. In most cases, infarction occurs when an atherosclerotic plaque fissures, ruptures or ulcerates and when conditions favor thrombogenesis. In rare cases, infarction may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, and a wide variety of systemic, particularly inflammatory diseases.

Although classical risk factors such as smoking, hyperlipidemia, hypertension, and diabetes are associated with many cases of coronary heart disease (CHD) and MI, many patients do not have involvement of these risk factors. In fact, many patients who exhibit one or more of these risk factors do not develop MI. Family history has long been recognized as one of the major risk factors. Although some of the familial clustering of MI reflects the genetic contribution to the other conventional risk factors, a large number of studies have suggested that there are significant genetic susceptibility factors, beyond those of the known risk factors (Friedlander Y, *et al., Br Heart J.* 1985; 53:382-7, Shea S. *et al., J. Am. Coll. Cardiol.* 1984; 4:793-801, and Hopkins P.N., *et al., Am. J. Cardiol.* 1988; 62:703-7). Major genetic susceptibility factors have not yet been identified.

SUMMARY OF THE INVENTION

As described herein, a locus on chromosome 13q12 has been identified as playing a major role in Myocardial Infarction (MI). The locus, herein after referred to as the MI locus, comprises nucleic acid that encodes 5-lipoxygenase activating protein (ALOX5AP or FLAP), herein after referred to as FLAP.

The present invention relates to isolated nucleic acid molecules comprising a portion or the entire human FLAP nucleic acid or a variant thereof. In one embodiment, the nucleic acid molecule has at least one polymorphism that is correlated with the incidence of myocardial infarction. The invention also relates to pathways targeting for drug delivery. A further embodiment of the invention is a method for the diagnosis of MI and a method for identification of susceptibility to myocardial infarction, by identifying polymorphisms in the FLAP nucleic acid, which identify those at risk. Also, described are haplotypes and SNPs that can be used to identify individuals with MI or at risk of developing MI. The polymorphism in the FLAP nucleic acid can be indicated by detecting the presence of a haplotype, comprising one or more of the markers: DG00AAFIU, SG13S25, DG00AAJFF, DG00AAHII, DG00AAHID, B_SNP_310657, SG13S30, SG13S32, SG13S42, and SG13S35 at the 13q12 locus comprising a FLAP nucleic acid. The polymorphism further can comprise at least one of the polymorphisms as indicated in Table 3.

Identification of nucleic acids and polymorphisms in the MI locus can pave the way for a better understanding of the disease process, which in turn can lead to improved diagnostic and therapeutic methods.

The invention further pertains to methods of diagnosing myocardial infarction or a susceptibility to myocardial infarction, comprising detecting an alteration in the expression or composition of a polypeptide encoded by a FLAP nucleic acid in a test sample, in comparison with the expression or composition of a polypeptide encoded by FLAP in a control sample, wherein the presence of an alteration in expression or composition of the polypeptide in the test sample is indicative of myocardial infarction or a susceptibility to myocardial infarction.

The invention also relates to an isolated nucleic acid molecule comprising a FLAP nucleic acid, wherein the FLAP nucleic acid has a nucleic acid sequence of

SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of SEQ ID NO: 1 or SEQ ID NO: 3, wherein the nucleic acid molecule comprises a polymorphism as indicated in Table 3.

In another embodiment, the invention relates to an isolated nucleic acid molecule having a polymorphism as indicated in Table 3, which hybridizes under high stringency conditions to a nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of SEQ ID NO: 1 or SEQ ID NO: 3.

In yet another embodiment, a method for assaying for the presence of a first nucleic acid molecule in a sample is described, comprising contacting said sample with a second nucleic acid molecule, where the second nucleic acid molecule comprises a nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3, and hybridizes to the first nucleic acid under high stringency conditions.

The invention also relates to a vector comprising an isolated nucleic acid molecule of the invention operably linked to a regulatory sequence, as well as to a recombinant host cell comprising the vector. The invention also provides a method for preparing a polypeptide encoded by an isolated nucleic acid molecule comprising culturing the recombinant host cell under conditions suitable for expression of said nucleic acid molecule.

Also contemplated by the invention is a method of assaying a sample for the presence of a polypeptide encoded by an isolated nucleic acid molecule of the invention, comprising contacting the sample with an antibody that specifically binds to the polypeptide.

The invention further provides a method of identifying an agent that alters expression of a FLAP nucleic acid, comprising: contacting a solution containing a nucleic acid comprising the promoter region of the FLAP nucleic acid operably linked to a reporter gene with an agent to be tested; assessing the level of expression of the reporter gene; and comparing the level of expression with a level of expression of the reporter gene in the absence of the agent; wherein if the level of expression of the reporter gene in the presence of the agent differs, by an amount that is statistically significant, from the level of expression in the absence of the agent, then the agent is

an agent that alters expression of the FLAP nucleic acid. An agent identified by this method is also contemplated.

The invention additionally comprises a method of identifying an agent that alters expression of a FLAP nucleic acid, in which a solution containing a nucleic acid described herein or a derivative or fragment thereof is contacted with an agent to be tested, and expression of the nucleic acid, derivative or fragment in the presence of the agent is assessed and compared with expression of the nucleic acid, derivative or fragment in the absence of the agent. If expression of the nucleic acid, derivative or fragment in the presence of the agent differs, by an amount that is statistically significant, from the expression in the absence of the agent, then the agent is an agent that alters expression of the FLAP nucleic acid. In certain embodiments, the expression of the nucleic acid, derivative or fragment in the presence of the agent comprises expression of one or more splicing variant(s) that differ in kind or in quantity from the expression of one or more splicing variant(s) the absence of the agent. Agents identified by this method are also contemplated. Representative agents include antisense nucleic acid to a FLAP nucleic acid; a FLAP polypeptide; a FLAP nucleic acid receptor; a FLAP nucleic acid binding agent; a peptidomimetic; a fusion protein; a prodrug thereof; an antibody; and a ribozyme. A method of altering expression of a FLAP nucleic acid comprising contacting a cell containing a FLAP nucleic acid with such an agent is also contemplated.

The invention further pertains to a method of identifying a polypeptide which interacts with a FLAP polypeptide, employing a yeast two-hybrid system that uses a first vector which comprises a nucleic acid encoding a DNA binding domain and a FLAP polypeptide, splicing variant, or a fragment or derivative thereof, and a second vector which comprises a nucleic acid encoding a transcription activation domain and a nucleic acid encoding a test polypeptide. If transcriptional activation occurs in the yeast two-hybrid system, the test polypeptide is a polypeptide which interacts with a FLAP polypeptide.

In a further embodiment, the invention relates to a myocardial infarction therapeutic agent, such as a FLAP nucleic acid or fragment or derivative thereof; a 5-lipoxygenase nucleic acid or fragment or derivative thereof; a leukotriene synthetase

nucleic acid or fragment or derivative thereof; a polypeptide encoded by a FLAP nucleic acid; a polypeptide encoded by a 5-lipoxygenase nucleic acid; a polypeptide encoded by a leukotriene synthetase nucleic acid; a FLAP receptor; a 5-lipoxygenase receptor; a leukotriene synthetase receptor; a FLAP nucleic acid binding agent; a 5-lipoxygenase binding agent; a leukotriene synthetase binding agent; a FLAP nucleic acid binding agent; a 5-liopoxygenase nucleic acid binding agent; a leukotriene synthetase nucleic acid binding agent; a peptidomimetic; a fusion protein; a prodrug; an antibody; an agent that alters FLAP nucleic acid expression; an agent that alters activity of a polypeptide encoded by a FLAP nucleic acid, a 5-lipoxygenase nucleic acid, or a leukotriene synthetase nucleic acid; an agent that alters posttranscriptional processing of a polypeptide encoded by a FLAP nucleic acid, a 5-lipoxygenase nucleic acid or a leukotriene synthetase nucleic acid; an agent that alters interaction of a FLAP nucleic acid with a FLAP nucleic acid binding agent; an agent that alters interaction of a 5-lipoxygenase nucleic acid with a 5-lipoxygenase nucleic acid binding agent; an agent that alters interaction of a leukotriene synthetase nucleic acid with a leukotriene synthetase nucleic acid binding agent; an agent that alters transcription of splicing variants encoded by a FLAP nucleic acid, a 5-lipoxygenase nucleic acid, or a leukotriene synthetase nucleic acid; or ribozymes; and pharmaceutical compositions comprising at least one myocardial infarction therapeutic agent.

The invention also pertains to a method of treating a disease or condition associated with FLAP in an individual, comprising administering a myocardial infarction therapeutic agent to the individual, in a therapeutically effective amount. In certain embodiments, the myocardial infarction therapeutic agent is a FLAP nucleic acid agonist or a FLAP nucleic acid antagonist.

A transgenic animal comprising a nucleic acid of the invention such as an exogenous FLAP nucleic acid or a nucleic acid encoding a FLAP polypeptide is also contemplated.

In yet another embodiment, the invention relates to a method for assaying a sample for the presence of a FLAP nucleic acid, by contacting the sample with a nucleic acid comprising a contiguous nucleic acid sequence which is at least partially

complementary to a part of the sequence of said FLAP nucleic acid, under conditions appropriate for hybridization, and assessing whether hybridization has occurred between a FLAP nucleic acid and said nucleic acid, wherein if hybridization has occurred, a FLAP nucleic acid is present in the nucleic acid. In certain embodiments, the contiguous nucleic acid sequence is completely complementary to a part of the sequence of said FLAP nucleic acid and in other embodiments; amplification is of at least part of said FLAP nucleic acid.

In certain embodiments, the contiguous nucleic acid sequence is 100 or fewer nucleotides in length and is either: a) at least 80% identical to a contiguous sequence of nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3; b) at least 80% identical to the complement of a contiguous sequence of nucleotides in of SEQ ID NO: 1 or SEQ ID NO: 3; or c) capable of selectively hybridizing to said FLAP nucleic acid.

The invention also pertains to a reagent for assaying a sample for the presence of a FLAP nucleic acid, the reagent comprising a nucleic acid comprising a contiguous nucleic acid sequence which is at least partially complementary to a part of the nucleic acid sequence of said FLAP nucleic acid. The reagent can comprise a contiguous nucleotide sequence which is completely complementary to a part of the nucleic acid sequence of said FLAP nucleic acid. A reagent kit for assaying a sample for the presence of a FLAP nucleic acid is also described, including (*e.g.*, in separate containers), one or more labeled nucleic acids comprising a contiguous nucleic acid sequence which is at least partially complementary to a part of the nucleic acid sequence of said FLAP nucleic acid; and reagents for detection of said label. The labeled nucleic acid can comprise a contiguous nucleotide sequence which is completely complementary to a part of the nucleic acid sequence of said FLAP nucleic acid. Also described herein is a reagent kit for assaying a sample for the presence of a FLAP nucleic acid, comprising one or more nucleic acids comprising a contiguous nucleic acid sequence which is at least partially complementary to a part of the nucleic acid sequence of said FLAP nucleic acid, and which is capable of acting as a primer for said FLAP nucleic acid when maintained under conditions for primer extension.

The invention also provides for the use of a nucleic acid for assaying a sample for the presence of a FLAP nucleic acid, in which the nucleic acid is 100 or fewer nucleotides in length and is either: at least 80% identical to a contiguous sequence of nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3; at least 80% identical to the complement of a contiguous sequence of nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3; or capable of selectively hybridizing to said FLAP nucleic acid.

In yet another embodiment, the use of a first nucleic acid for assaying a sample for the presence of a FLAP nucleic acid that has at least one nucleotide difference from the first nucleic acid is described, in which the first nucleic acid is 100 or fewer nucleotides in length and which is either: at least 80% identical to a contiguous sequence of nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3 or one of the sequences shown in Table 3; at least 80% identical to the complement of a contiguous sequence of nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3 one of the sequences shown in Table 3; or capable of selectively hybridizing to said FLAP nucleic acid.

The invention also relates to a method of diagnosing a susceptibility to myocardial infarction in an individual, comprising determining the presence or absence in the individual of certain "haplotypes" (combinations of genetic markers); the presence of the haplotype is diagnostic of susceptibility to myocardial infarction. In one embodiment, a haplotype associated with a susceptibility to myocardial infarction comprises markers DG00AAFIU, SG13S25, DG00AAJFF, DG00AAHII, SG13S32 and SG13S35 at the 13q12 locus. In one particular embodiment, the presence of the alleles T, G, G, G, A and G at DG00AAFIU, SG13S25, DG00AAJFF, DG00AAHII, SG13S32 and SG13S35, respectively (the B6 haplotype), is diagnostic of susceptibility to myocardial infarction. In another embodiment, a haplotype associated with a susceptibility to myocardial infarction comprises markers DG00AAFIU, SG13S25, DG00AAHII, SG13S30 and SG13S42 at the 13q12 locus. In one particular embodiment, the presence of the alleles T, G, G, G and A at DG00AAFIU, SG13S25, DG00AAHII, SG13S30 and SG13S42, respectively (the B5 haplotype), is diagnostic of susceptibility to myocardial infarction. In a third embodiment, a haplotype associated with a susceptibility to myocardial infarction comprises markers SG13S25, DG00AAHII, SG13S30 and SG13S42 at the 13q12

locus. In one particular embodiment, the presence of the alleles G, G, G and A at SG13S25, DG00AAHII, SG13S30 and SG13S42 , respectively (the B4 haplotype), is diagnostic of susceptibility to myocardial infarction. In a fourth embodiment, a haplotype associated with a susceptibility to myocardial infarction comprises markers DG00AAFIU, SG13S25, DG00AAHID, B_SNP_310657 and SG13S32 at the 13q12 locus. In one particular embodiment, the presence of the alleles T, G, T, G and A at DG00AAFIU, SG13S25, DG00AAHID, B_SNP_310657 and SG13S32, respectively (the A5 haplotype), is diagnostic of susceptibility to myocardial infarction. In a fifth embodiment, a haplotype associated with a susceptibility to myocardial infarction comprises markers SG13S25, DG00AAHID, B_SNP_310657 and SG13S32 at the 13q12 locus. In one particular embodiment, the presence of the alleles G, T, G and A at SG13S25, DG00AAHID, B_SNP_310657 and SG13S32, respectively (the A4 haplotype), is diagnostic of susceptibility to myocardial infarction. The presence or absence of the haplotype can be determined by various methods, including, for example, using enzymatic amplification, restriction fragment length polymorphism analysis, sequence analysis or electrophoretic analysis of nucleic acid from the individual.

The invention also relates to a method of diagnosing a susceptibility to myocardial infarction in an individual, comprising: obtaining a nucleic acid sample from said individual; and analyzing the nucleic acid sample for the presence or absence of a haplotype using markers DG00AAFIU, SG13S25, DG00AAJFF, DG00AAHII, DG00AAHID, B_SNP_310657, SG13S30, SG13S32, SG13S42, and SG13S35 , with alleles T, G, G, G, T, G, G, A, A, G, respectively, at the 13q12 locus, wherein the presence of the haplotype is diagnostic for a susceptibility to myocardial infarction.

Also described herein is a method of diagnosing myocardial infarction or a susceptibility to myocardial infarction in an individual, comprising determining the presence or absence in the individual of a haplotype comprising one or more markers and/or single nucleotide polymorphisms as shown in Table 3 in the locus on chromosome 13q12 comprising a FLAP nucleic acid, wherein the presence of the

haplotype is diagnostic of myocardial infarction or of a susceptibility to myocariial infarction.

A method for the diagnosis and identification of susceptibility to miocardial infarction in an individual is also described, comprising: screening for an at-risk haplotype in the FLAP nucleic acid that is more frequently present in an individual susceptible to myocardial infarction compared to an individual who is not susceptible to myocardial infarction wherein the at-risk haplotype increases the risk significantly. In certain embodiments, the significant increase is at least about 20%, and in other embodiments, the significant increase is identified as an odds ratio of at least about 1.2.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of preferred embodiments of the invention.

FIG. 1 shows the multipoint non-parametric LOD scores for a framework marker map on chromosome 13. A LOD score suggestive of linkage of 2.5 was found at marker D13S289. The maker map for chromosome 13 that was used in the linkage analysis is shown in Table 1.

FIG. 2 shows LOD score results for the families after adding 14 markers to the candidate region. The inclusion of additional microsatellite markers increased the information on sharing by decent from 0.7 to 0.8, around the markers that gave the highest LOD scores. The marker map used in the second step of linkage anaysis is shown in Table 2.

FIG. 3A shows the results from a haplotype association analysis using 4 and 5 microsatellite markers. The *p*-value of the association is plotted on the y-axis and position of markers on the x-axis. Only haplotypes that show association with a *p*-value $< 10^{-5}$ are shown in the figure. The most significant microsatellite marker haplotype association is found using markers DG13S1103, DG13S166, DG13S1287, DG13S1061 and DG13S301, with alleles 4, 0, 2, 14 and 3, respectively (*p*-value of 1.02×10^{-7}). Carrier frequency of the haplotype is 7.3% in affected individuals and

0.3% in controls. These results are based on 437 patients and 721 controls. The area that is common to all the haploytypes shown in the figure includes only one gene, FLAP.

FIG. 3B shows the alleles of the makers defining the most significant microsatellite marker haplotypes. The area defined with a black square is a common area to all the most significantly associated haplotypes. The FLAP nucleic acid is located between makers DG13S166 and D13S1238. Two marker haplotype involving alleles 0 and –2 for markers DG13S166 and S13S1238, respectively, is found in excess in patients. Carrier frequency of this haploype is 27% in patients and 15.4% in controls (p-value 1 X 10^{-3})

FIG. 4 shows the markers and genes around the FLAP (ALOX5AP) gene.

FIG. 5 shows the relative location of key SNPs and exons of the ALOX5AP/FLAP gene. Haplotype length varies between 33 to 68 kb.

FIGs. 6A-6Y4 show the genomic sequence of the FLAP gene (SEQ ID NO: 1).

FIG. 7A shows the amino acid sequence of FLAP (SEQ ID NO:2) and the mRNA of FLAP (SEQ ID NO: 3)

FIGs. 7B-7V show the sequences of the FLAP nucleic acid flanking the SNPs that were identified by sequencing samples from patients (SEQ ID NOs: 398-535).

DETAILED DESCRIPTION OF THE INVENTION

Extensive genealogical information has been combined with powerful gene sharing methods to map a locus on chromosome 13q12 that is associated with myocardial infarction. Patients with myocardial infarction and controls were initially genotyped with microsatellite markers with an average spacing between markers of less than 100kb over the 12Mb candidate region. An epidemiological study of a population-based sample of MI patients demonstrated the relative risk for siblings of a female MI patient is significantly higher than the relative risk for siblings of a male proband (1.59 (CI 1.47 - 1.73) vs. 1.35 (CI 1.28 - 1.42)). The gender difference in risk of getting MI (males being more likely to get MI) also suggests somewhat different etiology between males and females, where MI in females might represent a more extreme phenotype. This study stratified the population according to sex to

determine the genetic causes of MI for males and females. The results of the genome wide search of genes that cause MI in Iceland is described. This linkage analysis resulted in linkage on chromosome 13q12.

Initial haplotype association analysis using 4 or 5 microsatellite markers that extended across the gene and were in excess in patients indicated that FLAP is a susceptibility gene for myocardial infarction. A region that is common to all the microsatellite haplotypes includes only one gene, the FLAP gene.

The FLAP nucleic acid encodes a 5-lipoxygenase activating protein, which, in combination with 5-lipoxygenase (5-LO), is required for leukotriene synthesis. Inhibitors of its function impede translocation of 5-lipoxygenase from the cytoplasm to the cell membrane and inhibit activation of 5-lipoxygenase. One other member of the leukotriene pathway, CysLT2 receptor, maps to chromosome 13q14.2 (53 cM on FIG. 2). The region of this gene shows excess sharing identical by decent (LOD score=1) in female MI patients. This indicates that CysLT2 receptor might also play a role in the pathogenesis of MI.

Mutations and/or polymorphisms within the FLAP nucleic acid show association with the disease and can be used for methods of diagnosis. Furthermore, the FLAP gene and other members of the leukotriene pathway, such as 5-LO, LTA4, LTB4, LTC4, LTD4 and CysLT2, are therapeutic targets for myocardial infarction.

NUCLEIC ACIDS OF THE INVENTION

FLAP Nucleic Acids, Portions and Variants

Accordingly, the invention pertains to isolated nucleic acid molecules comprising a human FLAP nucleic acid. The term, "FLAP nucleic acid," as used herein, refers to an isolated nucleic acid molecule encoding FLAP polypeptide. The FLAP nucleic acid molecules of the present invention can be RNA, for example, mRNA, or DNA, such as cDNA and genomic DNA. DNA molecules can be double-stranded or single-stranded; single stranded RNA or DNA can be either the coding, or sense strand or the non-coding, or antisense strand. The nucleic acid molecule can include all or a portion of the coding sequence of the gene or nucleic acid and can

further comprise additional non-coding sequences such as introns and non-coding 3' and 5' sequences (including regulatory sequences, for example).

For example, a FLAP nucleic acid can consist of SEQ ID NOs: 1 or 3 or the complement thereof, or to a portion or fragment of such an isolated nucleic acid molecule (*e.g.*, cDNA or the nucleic acid) that encodes FLAP polypeptide (*e.g.*, a polypeptide such as SEQ ID NO: 2). In a preferred embodiment, the isolated nucleic acid molecule comprises a nucleic acid molecule selected from the group consisting of SEQ ID NOs: 1 or 3, or their complement thereof.

Additionally, the nucleic acid molecules of the invention can be fused to a marker sequence, for example, a sequence that encodes a polypeptide to assist in isolation or purification of the polypeptide. Such sequences include, but are not limited to, those that encode a glutathione-S-transferase (GST) fusion protein and those that encode a hemagglutinin A (HA) polypeptide marker from influenza.

An "isolated" nucleic acid molecule, as used herein, is one that is separated from nucleic acids that normally flank the gene or nucleic acid sequence (as in genomic sequences) and/or has been completely or partially purified from other transcribed sequences (*e.g.*, as in an RNA library). For example, an isolated nucleic acid of the invention may be substantially isolated with respect to the complex cellular milieu in which it naturally occurs, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. In some instances, the isolated material will form part of a composition (for example, a crude extract containing other substances), buffer system or reagent mix. In other circumstances, the material may be purified to essential homogeneity, for example as determined by PAGE or column chromatography such as HPLC. In certain embodiments, an isolated nucleic acid molecule comprises at least about 50, 80 or 90% (on a molar basis) of all macromolecular species present. With regard to genomic DNA, the term "isolated" also can refer to nucleic acid molecules that are separated from the chromosome with which the genomic DNA is naturally associated. For example, the isolated nucleic acid molecule can contain less than about 5 kb, including but not limited to 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotides

which flank the nucleic acid molecule in the genomic DNA of the cell from which the nucleic acid molecule is derived.

The nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated. Thus, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleic acid molecules include recombinant DNA molecules in heterologous host cells, as well as partially or substantially purified DNA molecules in solution. "Isolated" nucleic acid molecules also encompass *in vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention. An isolated nucleic acid molecule or nucleic acid sequence can include a nucleic acid molecule or nucleic acid sequence that is synthesized chemically or by recombinant means. Therefore, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleotide sequences include recombinant DNA molecules in heterologous organisms, as well as partially or substantially purified DNA molecules in solution. *In vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention are also encompassed by "isolated" nucleotide sequences. Such isolated nucleotide sequences are useful in the manufacture of the encoded polypeptide, as probes for isolating homologous sequences (*e.g.*, from other mammalian species), for gene mapping (*e.g.*, by *in situ* hybridization with chromosomes), or for detecting expression of the nucleic acid in tissue (*e.g.*, human tissue), such as by Northern blot analysis.

The present invention also pertains to nucleic acid molecules which are not necessarily found in nature but which encode a FLAP polypeptide (*e.g.*, a polypeptide having an amino acid sequence comprising an amino acid sequence of SEQ ID NOs: 2), or another splicing variant of a FLAP polypeptide or polymorphic variant thereof. Thus, for example, DNA molecules that comprise a sequence that is different from the naturally occurring nucleic acid sequence but which, due to the degeneracy of the genetic code, encode a FLAP polypeptide of the present invention are also the subjects of this invention. The invention also encompasses nucleotide sequences encoding portions (fragments), or encoding variant polypeptides such as analogues or derivatives of a FLAP polypeptide. Such variants can be naturally occurring, such as

in the case of allelic variation or single nucleotide polymorphisms, or non-naturally-occurring, such as those induced by various mutagens and mutagenic processes. Intended variations include, but are not limited to, addition, deletion and substitution of one or more nucleotides that can result in conservative or non-conservative amino acid changes, including additions and deletions. Preferably the nucleotide (and/or resultant amino acid) changes are silent or conserved; that is, they do not alter the characteristics or activity of a FLAP polypeptide. In one preferred embodiment, the nucleotide sequences are fragments that comprise one or more polymorphic microsatellite markers. In another preferred embodiment, the nucleotide sequences are fragments that comprise one or more single nucleotide polymorphisms in a FLAP nucleic acid (*e.g.*, the single nucleotide polymorphisms set forth in Table 3, below).

Other alterations of the nucleic acid molecules of the invention can include, for example, labeling, methylation, internucleotide modifications such as uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoamidates, carbamates), charged linkages (*e.g.*, phosphorothioates, phosphorodithioates), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine, psoralen), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids). Also included are synthetic molecules that mimic nucleic acid molecules in the ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

The invention also pertains to nucleic acid molecules that hybridize under high stringency hybridization conditions, such as for selective hybridization, to a nucleic acid sequence described herein (*e.g.*, nucleic acid molecules which specifically hybridize to a nucleic acid sequence encoding polypeptides described herein, and, optionally, have an activity of the polypeptide). In one embodiment, the invention includes variants described herein which hybridize under high stringency hybridization conditions (*e.g.*, for selective hybridization) to a nucleic acid sequence comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1 or 3 or the complement thereof. In another embodiment, the invention includes variants described herein which hybridize under high stringency

hybridization conditions (*e.g.*, for selective hybridization) to a nucleic acid sequence encoding an amino acid sequence of SEQ ID NO: 2 or a polymorphic variant thereof. In a preferred embodiment, the variant that hybridizes under high stringency hybridizations has an activity of a FLAP.

Such nucleic acid molecules can be detected and/or isolated by specific hybridization (*e.g.*, under high stringency conditions). "Specific hybridization," as used herein, refers to the ability of a first nucleic acid to hybridize to a second nucleic acid in a manner such that the first nucleic acid does not hybridize to any nucleic acid other than to the second nucleic acid (*e.g.*, when the first nucleic acid has a higher similarity to the second nucleic acid than to any other nucleic acid in a sample wherein the hybridization is to be performed). "Stringency conditions" for hybridization is a term of art which refers to the incubation and wash conditions, *e.g.*, conditions of temperature and buffer concentration, which permit hybridization of a particular nucleic acid to a second nucleic acid; the first nucleic acid may be perfectly (*i.e.*, 100%) complementary to the second, or the first and second may share some degree of complementarity that is less than perfect (*e.g.*, 70%, 75%, 85%, 95%). For example, certain high stringency conditions can be used which distinguish perfectly complementary nucleic acids from those of less complementarity. "High stringency conditions", "moderate stringency conditions" and "low stringency conditions" for nucleic acid hybridizations are explained on pages 2.10.1-2.10.16 and pages 6.3.1-6.3.6 in *Current Protocols in Molecular Biology* (Ausubel, F.M. *et al.*, "*Current Protocols in Molecular Biology*", John Wiley & Sons, (1998), the entire teachings of which are incorporated by reference herein). The exact conditions which determine the stringency of hybridization depend not only on ionic strength (*e.g.*, 0.2X SSC, 0.1X SSC), temperature (*e.g.*, room temperature, 42°C, 68°C) and the concentration of destabilizing agents such as formamide or denaturing agents such as SDS, but also on factors such as the length of the nucleic acid sequence, base composition, percent mismatch between hybridizing sequences and the frequency of occurrence of subsets of that sequence within other non-identical sequences. Thus, equivalent conditions can be determined by varying one or more of these parameters while maintaining a similar degree of identity or similarity between the two nucleic acid molecules.

Typically, conditions are used such that sequences at least about 60%, at least about 70%, at least about 80%, at least about 90% or at least about 95% or more identical to each other remain hybridized to one another. By varying hybridization conditions from a level of stringency at which no hybridization occurs to a level at which hybridization is first observed, conditions which will allow a given sequence to hybridize (*e.g.*, selectively) with the most similar sequences in the sample can be determined.

Exemplary conditions are described in Krause, M.H. and S.A. Aaronson, *Methods in Enzymology* 200: 546-556 (1991), and in, Ausubel, *et al.*, "*Current Protocols in Molecular Biology*", John Wiley & Sons, (1998), which describes the determination of washing conditions for moderate or low stringency conditions. Washing is the step in which conditions are usually set so as to determine a minimum level of complementarity of the hybrids. Generally, starting from the lowest temperature at which only homologous hybridization occurs, each °C by which the final wash temperature is reduced (holding SSC concentration constant) allows an increase by 1% in the maximum extent of mismatching among the sequences that hybridize. Generally, doubling the concentration of SSC results in an increase in T_m of ~17°C. Using these guidelines, the washing temperature can be determined empirically for high, moderate or low stringency, depending on the level of mismatch sought.

For example, a low stringency wash can comprise washing in a solution containing 0.2X SSC/0.1% SDS for 10 minutes at room temperature; a moderate stringency wash can comprise washing in a prewarmed solution (42°C) solution containing 0.2X SSC/0.1% SDS for 15 minutes at 42°C; and a high stringency wash can comprise washing in prewarmed (68°C) solution containing 0.1X SSC/0.1%SDS for 15 minutes at 68°C. Furthermore, washes can be performed repeatedly or sequentially to obtain a desired result as known in the art. Equivalent conditions can be determined by varying one or more of the parameters given as an example, as known in the art, while maintaining a similar degree of identity or similarity between the target nucleic acid molecule and the primer or probe used.

The percent homology or identity of two nucleotide or amino acid sequences can be determined by aligning the sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first sequence for optimal alignment). The nucleotides or amino acids at corresponding positions are then compared, and the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions x 100). When a position in one sequence is occupied by the same nucleotide or amino acid residue as the corresponding position in the other sequence, then the molecules are homologous at that position. As used herein, nucleic acid or amino acid "homology" is equivalent to nucleic acid or amino acid "identity". In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, for example, at least 40%, in certain embodiments at least 60%, and in other embodiments at least 70%, 80%, 90% or 95% of the length of the reference sequence. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A preferred, non-limiting example of such a mathematical algorithm is described in Karlin *et al.*, *Proc. Natl. Acad. Sci. USA* 90:5873-5877 (1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) as described in Altschul *et al.*, *Nucleic Acids Res.* 25:389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, NBLAST) can be used. In one embodiment, parameters for sequence comparison can be set at score=100, wordlength=12, or can be varied (*e.g.*, W=5 or W=20).

Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, *CABIOS* 4(1): 11-17 (1988). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package (Accelrys, Cambridge, UK). When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Additional algorithms for sequence analysis are known in the art and include ADVANCE and ADAM as described in Torellis and Robotti,

Comput. Appl. Biosci. 10:3-5 (1994); and FASTA described in Pearson and Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444-8 (1988).

In another embodiment, the percent identity between two amino acid sequences can be accomplished using the GAP program in the GCG software package using either a BLOSUM63 matrix or a PAM250 matrix, and a gap weight of 12, 10, 8, 6, or 4 and a length weight of 2, 3, or 4. In yet another embodiment, the percent identity between two nucleic acid sequences can be accomplished using the GAP program in the GCG software package using a gap weight of 50 and a length weight of 3.

The present invention also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleic acid sequence comprising SEQ ID NO: 1 or 3 or the complement of SEQ ID NO: 1 or 3, and also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleic acid sequence encoding an amino acid sequence of the invention or polymorphic variant thereof. The nucleic acid fragments of the invention are at least about 15, for example, at least about 18, 20, 23 or 25 nucleotides, and can be 30, 40, 50, 100, 200 or more nucleotides in length. Longer fragments, for example, 30 or more nucleotides in length, encoding antigenic polypeptides described herein are particularly useful, such as for the generation of antibodies as described below.

Probes and Primers

In a related aspect, the nucleic acid fragments of the invention are used as probes or primers in assays such as those described herein. "Probes" or "primers" are oligonucleotides that hybridize in a base-specific manner to a complementary strand of nucleic acid molecules. Such probes and primers include polypeptide nucleic acids, as described in Nielsen *et al.(Science* 254:1497-1500 (1991)).

A probe or primer comprises a region of nucleic acid that hybridizes to at least about 15, for example about 20-25, and in certain embodiments about 40, 50 or 75, consecutive nucleotides of a nucleic acid of the invention, such as a nucleic acid comprising a contiguous nucleic acid sequence of SEQ ID NOs: 1 or 3 or the

complement of SEQ ID Nos: 1 or 3, or a nucleic acid sequence encoding an amino acid sequence of SEQ ID NO: 2 or polymorphic variant thereof. In preferred embodiments, a probe or primer comprises 100 or fewer nucleotides, in certain embodiments, from 6 to 50 nucleotides, for example, from 12 to 30 nucleotides. In other embodiments, the probe or primer is at least 70% identical to the contiguous nucleic acid sequence or to the complement of the contiguous nucleotide sequence, for example, at least 80% identical, in certain embodiments at least 90% identical, and in other embodiments at least 95% identical, or even capable of selectively hybridizing to the contiguous nucleic acid sequence or to the complement of the contiguous nucleotide sequence. Often, the probe or primer further comprises a label, *e.g.*, radioisotope, fluorescent compound, enzyme, or enzyme co-factor.

The nucleic acid molecules of the invention such as those described above can be identified and isolated using standard molecular biology techniques and the sequence information provided herein. For example, nucleic acid molecules can be amplified and isolated using the polymerase chain reaction and synthetic oligonucleotide primers based on one or more of SEQ ID NOs: 1 or 3, or the complement thereof, or designed based on nucleotides based on sequences encoding one or more of the amino acid sequences provided herein. See generally *PCR Technology: Principles and Applications for DNA Amplification* (ed. H.A. Erlich, Freeman Press, NY, NY, 1992); *PCR Protocols: A Guide to Methods and Applications* (Eds. Innis *et al.*, Academic Press, San Diego, CA, 1990); Mattila *et al.*, *Nucl. Acids Res.* 19:4967 (1991); Eckert *et al.*, *PCR Methods and Applications* 1:17 (1991); PCR (eds. McPherson *et al.*, IRL Press, Oxford); and U.S. Patent 4,683,202. The nucleic acid molecules can be amplified using cDNA, mRNA or genomic DNA as a template, cloned into an appropriate vector and characterized by DNA sequence analysis.

Other suitable amplification methods include the ligase chain reaction (LCR) (see Wu and Wallace, *Genomics* 4:560 (1989), Landegren *et al.*, *Science* 241:1077 (1988), transcription amplification (Kwoh *et al.*, *Proc. Natl. Acad. Sci. USA* 86:1173 (1989)), and self-sustained sequence replication (Guatelli *et al.*, *Proc. Nat. Acad. Sci. USA* 87:1874 (1990)) and nucleic acid based sequence amplification (NASBA). The

latter two amplification methods involve isothermal reactions based on isothermal transcription, which produce both single stranded RNA (ssRNA) and double stranded DNA (dsDNA) as the amplification products in a ratio of about 30 or 100 to 1, respectively.

The amplified DNA can be labeled, for example, radiolabeled, and used as a probe for screening a cDNA library derived from human cells, mRNA in zap express, ZIPLOX or other suitable vector. Corresponding clones can be isolated, DNA can obtained following *in vivo* excision, and the cloned insert can be sequenced in either or both orientations by art recognized methods to identify the correct reading frame encoding a polypeptide of the appropriate molecular weight. For example, the direct analysis of the nucleic acid molecules of the present invention can be accomplished using well-known methods that are commercially available. See, for example, Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (2nd Ed., CSHP, New York 1989); Zyskind *et al.*, *Recombinant DNA Laboratory Manual*, (Acad. Press, 1988)). Using these or similar methods, the polypeptide and the DNA encoding the polypeptide can be isolated, sequenced and further characterized.

Antisense nucleic acid molecules of the invention can be designed using the nucleotide sequences of SEQ ID NOs: 1 or 3 and/or the complement of one or more of SEQ ID NOs: 1 or 3 and/or a portion of one or more of SEQ ID NOs: 1 or 3 or the complement of one or more of SEQ ID NOs: 1 or 3 and/or a sequence encoding the amino acid sequences of SEQ ID NOs: 2 or encoding a portion of one or more of SEQ ID NOs: 1 or 3 or their complement. They can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid molecule (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Alternatively, the antisense nucleic acid molecule can be produced biologically using an expression vector into which a nucleic acid molecule has been subcloned in

an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid molecule will be of an antisense orientation to a target nucleic acid of interest).

The nucleic acid sequences can also be used to compare with endogenous DNA sequences in patients to identify one or more of the disorders related to FLAP, and as probes, such as to hybridize and discover related DNA sequences or to subtract out known sequences from a sample. The nucleic acid sequences can further be used to derive primers for genetic fingerprinting, to raise anti-polypeptide antibodies using DNA immunization techniques, and as an antigen to raise anti-DNA antibodies or elicit immune responses. Portions or fragments of the nucleotide sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions or nucleic acid regions associated with genetic disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. Additionally, the nucleotide sequences of the invention can be used to identify and express recombinant polypeptides for analysis, characterization or therapeutic use, or as markers for tissues in which the corresponding polypeptide is expressed, either constitutively, during tissue differentiation, or in diseased states. The nucleic acid sequences can additionally be used as reagents in the screening and/or diagnostic assays described herein, and can also be included as components of kits (*e.g.*, reagent kits) for use in the screening and/or diagnostic assays described herein.

Vectors

Another aspect of the invention pertains to nucleic acid constructs containing a nucleic acid molecule of SEQ ID NOs: 1 or 3 or the complement thereof (or a portion thereof). Yet another aspect of the invention pertains to nucleic acid constructs containing a nucleic acid molecule encoding an amino acid of SEQ ID NO: 2 or polymorphic variant thereof. The constructs comprise a vector (*e.g.*, an expression vector) into which a sequence of the invention has been inserted in a sense or antisense orientation. As used herein, the term "vector" refers to a nucleic acid

molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, such as expression vectors, are capable of directing the expression of genes or nucleic acids to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses) that serve equivalent functions.

Preferred recombinant expression vectors of the invention comprise a nucleic acid molecule of the invention in a form suitable for expression of the nucleic acid molecule in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" or "operatively linked" is intended to mean that the nucleic acid sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleic acid sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, "Gene Expression Technology", *Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleic acid sequence in many types of host cell and those which direct expression of the nucleic acid sequence only in certain host cells (*e.g.*, tissue-specific

regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed and the level of expression of polypeptide desired. The expression vectors of the invention can be introduced into host cells to thereby produce polypeptides, including fusion polypeptides, encoded by nucleic acid molecules as described herein.

The recombinant expression vectors of the invention can be designed for expression of a polypeptide of the invention in prokaryotic or eukaryotic cells, *e.g.*, bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, a nucleic acid molecule of the invention can be expressed in bacterial cells (*e.g.*, *E. coli*), insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing a foreign nucleic acid molecule (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for

transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene or nucleic acid that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene or nucleic acid of interest. Preferred selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid molecules encoding a selectable marker can be introduced into a host cell on the same vector as the nucleic acid molecule of the invention or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid molecule can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene or nucleic acid will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic host cell or eukaryotic host cell in culture can be used to produce (*i.e.*, express) a polypeptide of the invention. Accordingly, the invention further provides methods for producing a polypeptide using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding a polypeptide of the invention has been introduced) in a suitable medium such that the polypeptide is produced. In another embodiment, the method further comprises isolating the polypeptide from the medium or the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a nucleic acid molecule of the invention has been introduced (*e.g.*, an exogenous FLAP nucleic acid, or an exogenous nucleic acid encoding a FLAP polypeptide). Such host cells can then be used to create non-human transgenic animals in which exogenous nucleotide sequences have been introduced into the genome or homologous recombinant animals in which endogenous nucleotide sequences have been altered. Such animals are useful for studying the function and/or activity of the nucleic acid sequence and

polypeptide encoded by the sequence and for identifying and/or evaluating modulators of their activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal include a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens and amphibians. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Pat. No. 4,873,191 and in Hogan, *Manipulating the Mouse Embryo* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, *Current Opinion in BioTechnology* 2:823-829 (1991) and in PCT Publication Nos. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169. Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.*, *Nature* 385:810-813 (1997) and PCT Publication Nos. WO 97/07668 and WO 97/07669.

POLYPEPTIDES OF THE INVENTION

The present invention also pertains to isolated polypeptides encoded by FLAP nucleic acids ("FLAP polypeptides"), and fragments and variants thereof, as well as polypeptides encoded by nucleotide sequences described herein (*e.g.*, other splicing variants). The term "polypeptide" refers to a polymer of amino acids, and not to a

specific length; thus, peptides, oligopeptides and proteins are included within the definition of a polypeptide. As used herein, a polypeptide is said to be "isolated" or "purified" when it is substantially free of cellular material when it is isolated from recombinant and non-recombinant cells, or free of chemical precursors or other chemicals when it is chemically synthesized. A polypeptide, however, can be joined to another polypeptide with which it is not normally associated in a cell (*e.g.*, in a "fusion protein") and still be "isolated" or "purified."

The polypeptides of the invention can be purified to homogeneity. It is understood, however, that preparations in which the polypeptide is not purified to homogeneity are useful. The critical feature is that the preparation allows for the desired function of the polypeptide, even in the presence of considerable amounts of other components. Thus, the invention encompasses various degrees of purity. In one embodiment, the language "substantially free of cellular material" includes preparations of the polypeptide having less than about 30% (by dry weight) other proteins (*i.e.*, contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins.

When a polypeptide is recombinantly produced, it can also be substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, less than about 10%, or less than about 5% of the volume of the polypeptide preparation. The language "substantially free of chemical precursors or other chemicals" includes preparations of the polypeptide in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of the polypeptide having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

In one embodiment, a polypeptide of the invention comprises an amino acid sequence encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1 or 3, or the complement of SEQ ID NO: 1 or 3, or portions thereof, or a portion or polymorphic variant thereof.

However, the polypeptides of the invention also encompass fragment and sequence variants. Variants include a substantially homologous polypeptide encoded by the same genetic locus in an organism, *i.e.*, an allelic variant, as well as other splicing variants. Variants also encompass polypeptides derived from other genetic loci in an organism, but having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1 or 3 or their complement, or portions thereof, or having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of nucleotide sequences encoding SEQ ID NO: 2 or polymorphic variants thereof. Variants also include polypeptides substantially homologous or identical to these polypeptides but derived from another organism, *i.e.*, an ortholog. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by chemical synthesis. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by recombinant methods.

As used herein, two polypeptides (or a region of the polypeptides) are substantially homologous or identical when the amino acid sequences are at least about 45-55%, in certain embodiments at least about 70-75%, and in other embodiments at least about 80-85%, and in others greater than about 90% or more homologous or identical. A substantially homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid molecule hybridizing to SEQ ID NO: 1 or 3 or portion thereof, under stringent conditions as more particularly described above, or will be encoded by a nucleic acid molecule hybridizing to a nucleic acid sequence encoding SEQ ID NO: 2 or a portion thereof or polymorphic variant thereof, under stringent conditions as more particularly described thereof.

The invention also encompasses polypeptides having a lower degree of identity but having sufficient similarity so as to perform one or more of the same functions performed by a polypeptide encoded by a nucleic acid molecule of the invention. Similarity is determined by conserved amino acid substitution. Such substitutions are those that substitute a given amino acid in a polypeptide by another

amino acid of like characteristics. Conservative substitutions are likely to be phenotypically silent. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the aromatic residues Phe and Tyr. Guidance concerning which amino acid changes are likely to be phenotypically silent are found in Bowie *et al.*, *Science* 247:1306-1310 (1990).

A variant polypeptide can differ in amino acid sequence by one or more substitutions, deletions, insertions, inversions, fusions, and truncations or a combination of any of these. Further, variant polypeptides can be fully functional or can lack function in one or more activities. Fully functional variants typically contain only conservative variation or variation in non-critical residues or in non-critical regions. Functional variants can also contain substitution of similar amino acids that result in no change or an insignificant change in function. Alternatively, such substitutions may positively or negatively affect function to some degree. Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, or truncation or a substitution, insertion, inversion, or deletion in a critical residue or critical region.

Amino acids that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham *et al.*, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity *in vitro*, or *in vitro* proliferative activity. Sites that are critical for polypeptide activity can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith *et al.*, *J. Mol. Biol. 224*:899-904 (1992); de Vos *et al.*, *Science 255*:306-312 (1992)).

The invention also includes fragments of the polypeptides of the invention. Fragments can be derived from a polypeptide encoded by a nucleic acid molecule comprising SEQ ID NO: 1 or 3, or the complement of SEQ ID NO: 1 or 3 (or other

variants). However, the invention also encompasses fragments of the variants of the polypeptides described herein. As used herein, a fragment comprises at least 6 contiguous amino acids. Useful fragments include those that retain one or more of the biological activities of the polypeptide as well as fragments that can be used as an immunogen to generate polypeptide-specific antibodies.

Biologically active fragments (peptides which are, for example, 6, 9, 12, 15, 16, 20, 30, 35, 36, 37, 38, 39, 40, 50, 100 or more amino acids in length) can comprise a domain, segment, or motif that has been identified by analysis of the polypeptide sequence using well-known methods, *e.g.*, signal peptides, extracellular domains, one or more transmembrane segments or loops, ligand binding regions, zinc finger domains, DNA binding domains, acylation sites, glycosylation sites, or phosphorylation sites.

Fragments can be discrete (not fused to other amino acids or polypeptides) or can be within a larger polypeptide. Further, several fragments can be comprised within a single larger polypeptide. In one embodiment a fragment designed for expression in a host can have heterologous pre- and pro-polypeptide regions fused to the amino terminus of the polypeptide fragment and an additional region fused to the carboxyl terminus of the fragment.

The invention thus provides chimeric or fusion polypeptides. These comprise a polypeptide of the invention operatively linked to a heterologous protein or polypeptide having an amino acid sequence not substantially homologous to the polypeptide. "Operatively linked" indicates that the polypeptide and the heterologous protein are fused in-frame. The heterologous protein can be fused to the N-terminus or C-terminus of the polypeptide. In one embodiment the fusion polypeptide does not affect function of the polypeptide *per se*. For example, the fusion polypeptide can be a GST-fusion polypeptide in which the polypeptide sequences are fused to the C-terminus of the GST sequences. Other types of fusion polypeptides include, but are not limited to, enzymatic fusion polypeptides, for example beta-galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions and Ig fusions. Such fusion polypeptides, particularly poly-His fusions, can facilitate the purification of recombinant polypeptide. In certain host cells (*e.g.*, mammalian host cells),

expression and/or secretion of a polypeptide can be increased using a heterologous signal sequence. Therefore, in another embodiment, the fusion polypeptide contains a heterologous signal sequence at its N-terminus.

EP-A-O 464 533 discloses fusion proteins comprising various portions of immunoglobulin constant regions. The Fc is useful in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262). In drug discovery, for example, human proteins have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists. Bennett *et al.*, *Journal of Molecular Recognition, 8*:52-58 (1995) and Johanson *et al.*, *The Journal of Biological Chemistry, 270*,16:9459-9471 (1995). Thus, this invention also encompasses soluble fusion polypeptides containing a polypeptide of the invention and various portions of the constant regions of heavy or light chains of immunoglobulins of various subclasses (IgG, IgM, IgA, IgE).

A chimeric or fusion polypeptide can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of nucleic acid fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive nucleic acid fragments which can subsequently be annealed and re-amplified to generate a chimeric nucleic acid sequence (see Ausubel *et al.*, *Current Protocols in Molecular Biology*, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST protein). A nucleic acid molecule encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide.

The isolated polypeptide can be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant), or synthesized using known protein synthesis methods. In one embodiment, the polypeptide is produced by recombinant DNA techniques. For example, a nucleic acid molecule encoding the polypeptide is cloned into an expression vector, the expression vector

introduced into a host cell and the polypeptide expressed in the host cell. The polypeptide can then be isolated from the cells by an appropriate purification scheme using standard protein purification techniques.

The polypeptides of the present invention can be used to raise antibodies or to elicit an immune response. The polypeptides can also be used as a reagent, *e.g.*, a labeled reagent, in assays to quantitatively determine levels of the polypeptide or a molecule to which it binds (*e.g.*, a ligand) in biological fluids. The polypeptides can also be used as markers for cells or tissues in which the corresponding polypeptide is preferentially expressed, either constitutively, during tissue differentiation, or in diseased states. The polypeptides can be used to isolate a corresponding binding agent, *e.g.*, ligand, such as, for example, in an interaction trap assay, and to screen for peptide or small molecule antagonists or agonists of the binding interaction. For example, because members of the leukotriene pathway including FLAP bind to receptors, the leukotriene pathway polypeptides can be used to isolate such receptors.

ANTIBODIES OF THE INVENTION

Polyclonal and/or monoclonal antibodies that specifically bind one form of the polypeptide or nucleic acid product (*e.g.*, a polypeptide encoded by a nucleic acid having a SNP as set forth in Table 3), but not to another form of the polypeptide or nucleic acid product, are also provided. Antibodies are also provided which bind a portion of either polypeptide encoded by nucleic acids of the invention (*e.g.*, SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of SEQ ID NO: 1 or SEQ ID NO: 3), or to a polypeptide encoded by nucleic acids of the invention that contain a polymorphic site or sites. The invention also provides antibodies to the polypeptides and polypeptide fragments of the invention, or a portion thereof, or having an amino acid sequence encoded by a nucleic acid molecule comprising all or a portion of SEQ ID NOs: 1 or 3, or the complement thereof, or another variant or portion thereof. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that specifically binds an antigen. A molecule that specifically binds to a polypeptide of the invention is a molecule that binds to that

polypeptide or a fragment thereof, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the polypeptide. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and $F(ab')_2$ fragments which can be generated by treating the antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind to a polypeptide of the invention. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of a polypeptide of the invention. A monoclonal antibody composition thus typically displays a single binding affinity for a particular polypeptide of the invention with which it immunoreacts.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a desired immunogen, *e.g.*, polypeptide of the invention or fragment thereof. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules directed against the polypeptide can be isolated from the mammal (*e.g.*, from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, *e.g.*, when the antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, *Nature* 256:495-497 (1975), the human B cell hybridoma technique (Kozbor *et al.*, *Immunol. Today* 4:72 (1983)); the EBV-hybridoma technique (Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, 1985, Inc., pp. 77-96); or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology* (1994) Coligan *et al.* (eds.) John Wiley & Sons, Inc., New York, NY). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with an immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a

hybridoma producing a monoclonal antibody that binds a polypeptide of the invention.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating a monoclonal antibody to a polypeptide of the invention (see, *e.g.*, *Current Protocols in Immunology, supra*; Galfre *et al.*, *Nature* 266:55052 (1977); R.H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); and Lerner, *Yale J. Biol. Med.* 54:387-402 (1981). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods that also would be useful.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody to a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide to thereby isolate immunoglobulin library members that bind the polypeptide. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *Surf*ZAP™ Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.*, *Bio/Technology* 9: 1370-1372 (1991); Hay *et al.*, *Hum. Antibod. Hybridomas* 3:81-85 (1992); Huse *et al.*, *Science* 246:1275-1281 (1989); Griffiths *et al.*, *EMBO J.* 12:725-734 (1993).

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art.

In general, antibodies of the invention (*e.g.*, a monoclonal antibody) can be used to isolate a polypeptide of the invention by standard techniques, such as affinity chromatography or immunoprecipitation. A polypeptide-specific antibody can facilitate the purification of natural polypeptide from cells and of recombinantly produced polypeptide expressed in host cells. Moreover, an antibody specific for a polypeptide of the invention can be used to detect the polypeptide (*e.g.*, in a cellular lysate, cell supernatant, or tissue sample) in order to evaluate the abundance and pattern of expression of the polypeptide. Antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, ß-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

DIAGNOSTIC ASSAYS

The nucleic acids, probes, primers, polypeptides and antibodies described herein can be used in methods of diagnosis of MI or diagnosis of a susceptibility to MI or to a disease or condition associated with an MI gene, such as FLAP, as well as in kits useful for diagnosis of MI or a susceptibility to MI or to a disease or condition associated with FLAP. In one embodiment, the kit useful for diagnosis of MI or susceptibility to MI, or to a disease or condition associated with FLAP comprises primers as described herein, wherein the primers contain one or more of the SNPs identified in Table 3.

In one embodiment of the invention, diagnosis of MI or susceptibility to MI (or diagnosis of or susceptibility to a disease or condition associated with FLAP), is made by detecting a polymorphism in a FLAP nucleic acid as described herein. The polymorphism can be an alteration in a FLAP nucleic acid, such as the insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift alteration; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of the gene or nucleic acid; duplication of all or a part of the gene or nucleic acid; transposition of all or a part of the gene or nucleic acid; or rearrangement of all or a part of the gene or nucleic acid. More than one such alteration may be present in a single gene or nucleic acid. Such sequence changes cause an alteration in the polypeptide encoded by a FLAP nucleic acid. For example, if the alteration is a frame shift alteration, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a premature stop codon, causing generation of a truncated polypeptide. Alternatively, a polymorphism associated with a disease or condition associated with a FLAP nucleic acid or a susceptibility to a disease or condition associated with a FLAP nucleic acid can be a synonymous alteration in one or more nucleotides (*i.e.*, an alteration that does not result in a change in the polypeptide encoded by a FLAP nucleic acid). Such a polymorphism may alter splicing sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of the nucleic acid. A FLAP nucleic acid that has any of the alteration described above is referred to herein as an "altered nucleic acid."

In a first method of diagnosing MI or a susceptibility to MI, hybridization methods, such as Southern analysis, Northern analysis, or *in situ* hybridizations, can be used (see *Current Protocols in Molecular Biology*, Ausubel, F. *et al.*, eds., John Wiley & Sons, including all supplements through 1999). For example, a biological sample from a test subject (a "test sample") of genomic DNA, RNA, or cDNA, is

obtained from an individual suspected of having, being susceptible to or predisposed for, or carrying a defect for, a susceptibility to a disease or condition associated with a FLAP nucleic acid (the "test individual"). The individual can be an adult, child, or fetus. The test sample can be from any source which contains genomic DNA, such as a blood sample, sample of amniotic fluid, sample of cerebrospinal fluid, or tissue sample from skin, muscle, buccal or conjunctival mucosa, placenta, gastrointestinal tract or other organs. A test sample of DNA from fetal cells or tissue can be obtained by appropriate methods, such as by amniocentesis or chorionic villus sampling. The DNA, RNA, or cDNA sample is then examined to determine whether a polymorphism in a nucleic acid is present, and/or to determine which splicing variant(s) encoded by the FLAP is present. The presence of the polymorphism or splicing variant(s) can be indicated by hybridization of the nucleic acid in the genomic DNA, RNA, or cDNA to a nucleic acid probe. A "nucleic acid probe", as used herein, can be a DNA probe or an RNA probe; the nucleic acid probe can contain at least one polymorphism in a FLAP nucleic acid or contains a nucleic acid encoding a particular splicing variant of a FLAP nucleic acid. The probe can be any of the nucleic acid molecules described above (*e.g.*, the nucleic acid, a fragment, a vector comprising the nucleic acid, a probe or primer, etc.).

To diagnose MI or a susceptibility to MI (or a disease or condition associated with FLAP), the test sample containing a FLAP nucleic acid is contacted with at least one nucleic acid probe to form a hybridization sample. A preferred probe for detecting mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to mRNA or genomic DNA sequences described herein. The nucleic acid probe can be, for example, a full-length nucleic acid molecule, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to appropriate mRNA or genomic DNA. For example, the nucleic acid probe can be all or a portion of one of SEQ ID NOs: 1 and 3, or the complement thereof or a portion thereof; or can be a nucleic acid encoding all or a portion of one of SEQ ID NO: 2. Other suitable probes for use in the diagnostic assays of the invention are described above

(see *e.g.*, probes and primers discussed under the heading, "Nucleic Acids of the Invention").

The hybridization sample is maintained under conditions that are sufficient to allow specific hybridization of the nucleic acid probe to a FLAP nucleic acid. "Specific hybridization", as used herein, indicates exact hybridization (*e.g.*, with no mismatches). Specific hybridization can be performed under high stringency conditions or moderate stringency conditions, for example, as described above. In a particularly preferred embodiment, the hybridization conditions for specific hybridization are high stringency.

Specific hybridization, if present, is then detected using standard methods. If specific hybridization occurs between the nucleic acid probe and FLAP nucleic acid in the test sample, then the FLAP has the polymorphism, or is the splicing variant, that is present in the nucleic acid probe. More than one nucleic acid probe can also be used concurrently in this method. Specific hybridization of any one of the nucleic acid probes is indicative of a polymorphism in the FLAP nucleic acid, or of the presence of a particular splicing variant encoding the FLAP nucleic acid, and is therefore diagnostic for a disease or condition associated with FLAP or a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI).

In Northern analysis (see *Current Protocols in Molecular Biology*, Ausubel, F. *et al.*, eds., John Wiley & Sons, *supra*) the hybridization methods described above are used to identify the presence of a polymorphism or a particular splicing variant, associated with a disease or condition associated with or a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI). For Northern analysis, a test sample of RNA is obtained from the individual by appropriate means. Specific hybridization of a nucleic acid probe, as described above, to RNA from the individual is indicative of a polymorphism in a FLAP nucleic acid, or of the presence of a particular splicing variant encoded by a FLAP nucleic acid, and is therefore diagnostic for the disease or condition associated with FLAP, or for susceptibility to a disease or condition associated with FLAP (*e.g.*, MI).

For representative examples of use of nucleic acid probes, see, for example, U.S. Patents No. 5,288,611 and 4,851,330.

Alternatively, a peptide nucleic acid (PNA) probe can be used instead of a nucleic acid probe in the hybridization methods described above. PNA is a DNA mimic having a peptide-like, inorganic backbone, such as N-(2-aminoethyl)glycine units, with an organic base (A, G, C, T or U) attached to the glycine nitrogen via a methylene carbonyl linker (see, for example, Nielsen, P.E. *et al.*, *Bioconjugate Chemistry* 5, American Chemical Society, p. 1 (1994). The PNA probe can be designed to specifically hybridize to a nucleic acid having a polymorphism associated with a disease or condition associated with FLAP or associated with a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI). Hybridization of the PNA probe to a FLAP nucleic acid as described herein is diagnostic for the disease or condition or the susceptibility to the disease or condition.

In another method of the invention, mutation analysis by restriction digestion can be used to detect an altered nucleic acid, or nucleic acids containing a polymorphism(s), if the mutation or polymorphism in the nucleic acid results in the creation or elimination of a restriction site. A test sample containing genomic DNA is obtained from the individual. Polymerase chain reaction (PCR) can be used to amplify a FLAP nucleic acid (and, if necessary, the flanking sequences) in the test sample of genomic DNA from the test individual. RFLP analysis is conducted as described (see *Current Protocols in Molecular Biology*, *supra*). The digestion pattern of the relevant DNA fragment indicates the presence or absence of the alteration or polymorphism in the FLAP nucleic acid, and therefore indicates the presence or absence of a disease or condition associated with FLAP or the susceptibility to a disease or condition associated with FLAP (*e.g.*, MI).

Sequence analysis can also be used to detect specific polymorphisms in the FLAP nucleic acid. A test sample of DNA or RNA is obtained from the test individual. PCR or other appropriate methods can be used to amplify the nucleic acid, and/or its flanking sequences, if desired. The sequence of a FLAP nucleic acid, or a fragment of the nucleic acid, or cDNA, or fragment of the cDNA, or mRNA, or fragment of the mRNA, is determined, using standard methods. The sequence of the nucleic acid, nucleic acid fragment, cDNA, cDNA fragment, mRNA, or mRNA fragment is compared with the known nucleic acid sequence of the nucleic acid,

cDNA (*e.g.*, one or more of SEQ ID NOs: 1 or 3, and/or the complement of SEQ ID NO: 1 or 3), or a nucleic acid sequence encoding SEQ ID NO: 2 or a fragment thereof) or mRNA, as appropriate. The presence of a polymorphism in the FLAP indicates that the individual has disease or a susceptibility to a disease associated with FLAP (*e.g.*, MI).

Allele-specific oligonucleotides can also be used to detect the presence of polymorphism(s) in the FLAP nucleic acid, through the use of dot-blot hybridization of amplified oligonucleotides with allele-specific oligonucleotide (ASO) probes (see, for example, Saiki, R. *et al.*, *Nature* 324:163-166 (1986)). An "allele-specific oligonucleotide" (also referred to herein as an "allele-specific oligonucleotide probe") is an oligonucleotide of approximately 10-50 base pairs, for example, approximately 15-30 base pairs, that specifically hybridizes to a FLAP nucleic acid, and that contains a polymorphism associated with a disease or condition associated with FLAP or a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI). An allele-specific oligonucleotide probe that is specific for particular polymorphisms in a FLAP nucleic acid can be prepared, using standard methods (see *Current Protocols in Molecular Biology*, *supra*). To identify polymorphisms in the nucleic acid associated with disease or susceptibility to disease, a test sample of DNA is obtained from the individual. PCR can be used to amplify all or a fragment of a FLAP nucleic acid, and its flanking sequences. The DNA containing the amplified FLAP nucleic acid (or fragment of the nucleic acid) is dot-blotted, using standard methods (see *Current Protocols in Molecular Biology*, *supra*), and the blot is contacted with the oligonucleotide probe. The presence of specific hybridization of the probe to the amplified FLAP is then detected. Specific hybridization of an allele-specific oligonucleotide probe to DNA from the individual is indicative of a polymorphism in the FLAP, and is therefore indicative of a disease or condition associated with FLAP or a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI).

An allele-specific primer hybridizes to a site on target DNA overlapping a polymorphism and only primes amplification of an allelic form to which the primer exhibits perfect complementarity. See Gibbs, *Nucleic Acid Res.* 17, 2427-2448 (1989). This primer is used in conjunction with a second primer which hybridizes at a

distal site. Amplification proceeds from the two primers, resulting in a detectable product which indicates the particular allelic form is present. A control is usually performed with a second pair of primers, one of which shows a single base mismatch at the polymorphic site and the other of which exhibits perfect complementarity to a distal site. The single-base mismatch prevents amplification and no detectable product is formed. The method works best when the mismatch is included in the 3'-most position of the oligonucleotide aligned with the polymorphism because this position is most destabilizing to elongation from the primer (see, *e.g.,* WO 93/22456).

In another embodiment, arrays of oligonucleotide probes that are complementary to target nucleic acid sequence segments from an individual, can be used to identify polymorphisms in a FLAP nucleic acid. For example, in one embodiment, an oligonucleotide array can be used. Oligonucleotide arrays typically comprise a plurality of different oligonucleotide probes that are coupled to a surface of a substrate in different known locations. These oligonucleotide arrays, also described as "Genechips™," have been generally described in the art, for example, U.S. Pat. No. 5,143,854 and PCT patent publication Nos. WO 90/15070 and WO 92/10092. These arrays can generally be produced using mechanical synthesis methods or light directed synthesis methods that incorporate a combination of photolithographic methods and solid phase oligonucleotide synthesis methods. See Fodor *et al.*, *Science* 251:767-777 (1991); Pirrung *et al.*, U.S. Pat. 5,143,854; (see also PCT Application WO 90/15070); Fodor *et al.*, PCT Publication WO 92/10092; and U.S. Pat. 5,424,186, the entire teachings of each of which are incorporated by reference herein. Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, *e.g.*, U.S. Pat. 5,384,261, the entire teachings of which are incorporated by reference herein. In another example, linear arrays can be utilized.

Once an oligonucleotide array is prepared, a nucleic acid of interest is hybridized with the array and scanned for polymorphisms. Hybridization and scanning are generally carried out by methods described herein and also in, *e.g.*, published PCT Application Nos. WO 92/10092 and WO 95/11995, and U.S. Pat. No. 5,424,186, the entire teachings of which are incorporated by reference herein. In brief, a target nucleic acid sequence that includes one or more previously identified

polymorphic markers is amplified using well-known amplification techniques, *e.g.*, PCR. Typically, this involves the use of primer sequences that are complementary to the two strands of the target sequence both upstream and downstream from the polymorphism. Asymmetric PCR techniques may also be used. Amplified target, generally incorporating a label, is then hybridized with the array under appropriate conditions. Upon completion of hybridization and washing of the array, the array is scanned to determine the position on the array to which the target sequence hybridizes. The hybridization data obtained from the scan is typically in the form of fluorescence intensities as a function of location on the array. In a reverse method, a probe, containing a polymorphism, can be coupled to a solid surface and PCR amplicons are then added to hybridize to these probes.

Although primarily described in terms of a single detection block, *e.g.*, detection of a single polymorphism arrays can include multiple detection blocks, and thus be capable of analyzing multiple, specific polymorphisms. It will generally be understood that detection blocks may be grouped within a single array or in multiple, separate arrays so that varying, optimal conditions may be used during the hybridization of the target to the array. For example, it may often be desirable to provide for the detection of those polymorphisms that fall within G-C rich stretches of a genomic sequence, separately from those falling in A-T rich segments. This allows for the separate optimization of hybridization conditions for each situation.

Additional uses of oligonucleotide arrays for detection of polymorphisms can be found, for example, in U.S. Patents Nos. 5,858,659 and 5,837,832, the entire teachings of which are incorporated by reference herein. Other methods of nucleic acid analysis can be used to detect polymorphisms in a nucleic acid described herein, or variants encoded by a nucleic acid described herein. Representative methods include direct manual sequencing (Church and Gilbert, *Proc. Natl. Acad. Sci. USA* 81:1991-1995 (1988); Sanger, F. *et al.*, *Proc. Natl. Acad. Sci., USA* 74:5463-5467 (1977); Beavis *et al.* U.S. Pat. No. 5,288,644); automated fluorescent sequencing; single-stranded conformation polymorphism assays (SSCP); clamped denaturing gel electrophoresis (CDGE); denaturing gradient gel electrophoresis (DGGE) (Sheffield, V.C. *et al.*, *Proc. Natl. Acad. Sci. USA* 86:232-236 (1989)), mobility shift analysis

(Orita, M. *et al.*, *Proc. Natl. Acad. Sci. USA* 86:2766-2770 (1989)), restriction enzyme analysis (Flavell *et al.*, *Cell* 15:25 (1978); Geever, *et al.*, *Proc. Natl. Acad. Sci. USA* 78:5081 (1981)); heteroduplex analysis; chemical mismatch cleavage (CMC) (Cotton *et al.*, *Proc. Natl. Acad. Sci. USA* 85:4397-4401 (1985)); RNase protection assays (Myers, R.M. *et al.*, *Science* 230:1242 (1985)); use of polypeptides which recognize nucleotide mismatches, such as *E. coli* mutS protein; allele-specific PCR, for example.

In one embodiment of the invention, diagnosis of a disease or condition associated with FLAP (*e.g.*, MI) or a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI) can also be made by expression analysis by quantitative PCR (kinetic thermal cycling). This technique utilizing TaqMan ® can be used to allow the identification of polymorphisms and whether a patient is homozygous or heterozygous. The technique can assess the presence of an alteration in the expression or composition of the polypeptide encoded by a FLAP nucleic acid or splicing variants encoded by a FLAP nucleic acid. Further, the expression of the variants can be quantified as physically or functionally different.

In another embodiment of the invention, diagnosis of MI or a susceptibility to MI (or of another disease or condition associated with FLAP) can also be made by examining expression and/or composition of a FLAP polypeptide, by a variety of methods, including enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. A test sample from an individual is assessed for the presence of an alteration in the expression and/or an alteration in composition of the polypeptide encoded by a FLAP nucleic acid, or for the presence of a particular variant encoded by a FLAP nucleic acid. An alteration in expression of a polypeptide encoded by a FLAP nucleic acid can be, for example, an alteration in the quantitative polypeptide expression (*i.e.*, the amount of polypeptide produced); an alteration in the composition of a polypeptide encoded by a FLAP nucleic acid is an alteration in the qualitative polypeptide expression (*e.g.*, expression of an altered FLAP polypeptide or of a different splicing variant). In a preferred embodiment, diagnosis of disease or condition associated with FLAP or a susceptibility to a disease

or condition associated with FLAP is made by detecting a particular splicing variant encoded by that FLAP variant, or a particular pattern of splicing variants.

Both such alterations (quantitative and qualitative) can also be present. An "alteration" in the polypeptide expression or composition, refers to an alteration in expression or composition in a test sample, as compared with the expression or composition of polypeptide by a FLAP nucleic acid in a control sample. A control sample is a sample that corresponds to the test sample (*e.g.*, is from the same type of cells), and is from an individual who is not affected by the disease or a susceptibility to a disease or condition associated with a FLAP nucleic acid. An alteration in the expression or composition of the polypeptide in the test sample, as compared with the control sample, is indicative of disease or condition associated with FLAP or a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI). Similarly, the presence of one or more different splicing variants in the test sample, or the presence of significantly different amounts of different splicing variants in the test sample, as compared with the control sample, is indicative of a susceptibility to a disease or condition associated with a FLAP nucleic acid. Various means of examining expression or composition of the polypeptide encoded by a FLAP nucleic acid can be used, including: spectroscopy, colorimetry, electrophoresis, isoelectric focusing and immunoassays (*e.g.*, David *et al.*, U.S. Pat. 4,376,110) such as immunoblotting (see also *Current Protocols in Molecular Biology*, particularly Chapter 10). For example, in one embodiment, an antibody capable of binding to the polypeptide (*e.g.*, as described above), preferably an antibody with a detectable label, can be used. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or $F(ab')_2$) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

Western blotting analysis, using an antibody as described above that specifically binds to a polypeptide encoded by an altered FLAP (*e.g.*, by a FLAP having a SNP as shown in Table 3), or an antibody that specifically binds to a polypeptide encoded by a non-altered nucleic acid, or an antibody that specifically binds to a particular splicing variant encoded by a nucleic acid, can be used to identify the presence in a test sample of a particular splicing variant or of a polypeptide encoded by a polymorphic or altered FLAP, or the absence in a test sample of a particular splicing variant or of a polypeptide encoded by a non-polymorphic or non-altered nucleic acid. The presence of a polypeptide encoded by a polymorphic or altered nucleic acid, or the absence of a polypeptide encoded by a non-polymorphic or non-altered nucleic acid, is diagnostic for disease or condition associated with FLAP or a susceptibility to a disease or condition associated with, as is the presence (or absence) of particular splicing variants encoded by the FLAP nucleic acid.

In one embodiment of this method, the level or amount of polypeptide encoded by a FLAP nucleic acid in a test sample is compared with the level or amount of the polypeptide encoded by the FLAP in a control sample. A level or amount of the polypeptide in the test sample that is higher or lower than the level or amount of the polypeptide in the control sample, such that the difference is statistically significant, is indicative of an alteration in the expression of the polypeptide encoded by the FLAP, and is diagnostic for disease or condition, or for a susceptibility to a disease or condition, associated with that FLAP. Alternatively, the composition of the polypeptide encoded by a FLAP nucleic acid in a test sample is compared with the composition of the polypeptide encoded by the FLAP in a control sample (*e.g.*, the presence of different splicing variants). A difference in the composition of the polypeptide in the test sample, as compared with the composition of the polypeptide in the control sample, is diagnostic for a disease or condition, or for a susceptibility to a disease or condition, associated with that FLAP. In another embodiment, both the level or amount and the composition of the polypeptide can be assessed in the test sample and in the control sample. A difference in the amount or level of the polypeptide in the test sample, compared to the control sample; a difference in composition in the test sample, compared to the control sample; or both a difference

in the amount or level, and a difference in the composition, is indicative of a disease or condition, or a susceptibility to a disease or condition, associated with FLAP (*e.g.*, MI).

The invention further pertains to a method for the diagnosis and identification of susceptibility to myocardial infarction in an individual, by identifying an at-risk haplotype in FLAP. In one embodiment, the at-risk haplotype is one which confers a significant risk of MI. In one embodiment, significance associated with a haplotype is measured by an odds ratio. In a further embodiment, the significance is measured by a percentage. In one embodiment, a significant risk is measured as an odds ratio of at least about 1.2, including by not limited to: 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8 and 1.9. In a further embodiment, an odds ratio of at least 1.2 is significant. In a further embodiment, an odds ratio of at least about 1.5 is significant. In a further embodiment, a significant increase in risk is at least about 1.7 is significant. In a further embodiment, a significant increase in risk is at least about 20%, including but not limited to about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 98%. In a further embodiment, a significant increase in risk is at least about 50%. It is understood however, that identifying whether a risk is medically significant may also depend on a variety of factors, including the specific disease, the haplotype, and often, environmental factors.

The invention also pertains to methods of diagnosing myocardial infarction or a susceptibility to myocardial infarction in an individual, comprising screening for an at-risk haplotype in the FLAP nucleic acid that is more frequently present in an individual susceptible to myocardial infarction (affected), compared to the frequency of its presence in a healthy individual (control), wherein the presence of the haplotype is indicative of myocardial infarction or susceptibility to myocardial infarction. Standard techniques for genotyping for the presence of SNPs and/or microsatellite markers that are associated with myocardial infarction can be used, such as fluorescent based techniques (Chen, *et al.*, *Genome Res. 9*, 492 (1999), PCR, LCR, Nested PCR and other techniques for nucleic acid amplification. In a preferred embodiment, the method comprises assessing in an individual the presence or frequency of SNPs and/or microsatellites in the FLAP nucleic acid that are associated

with myocardial infarction, wherein an excess or higher frequency of the SNPs and/or microsatellites compared to a healthy control individual is indicative that the individual has myocardial infarction or is susceptible to myocardial infarction. See Table 3 that sets forth SNPs and markers for use as screening tools.

In one embodiment, the at-risk haplotype is characterized by the presence of polymorphism(s) represented in Table 3. For example, DG00AAFIU at position 256047, where the SNP can be a "C" or a "T"; SG13S25 at position 283477, where the SNP can be a "G" or an "A"; DG00AAJFF at position 287889, where the SNP can be a "G" or an "A"; DG00AAHII at position 294503, where the SNP can be a "G" or an "A"; DG00AAHID at position 296020, where the SNP can be a "T" or an "A"; B_SNP_310657 at position 310657, where the SNP can be a "G" or an "A"; SG13S30 at position 312056, where the SNP can be a "G" or a "T"; SG13S32 at position 316763, where the SNP can be a "C" or an "A"; SG13S42 at position 320393, where the SNP can be a "G" or an "A"; and SG13S35 at position 324333, where the SNP can be a "G" or an "A". Kits (*e.g.*, reagent kits) useful in the methods of diagnosis comprise components useful in any of the methods described herein, including for example, hybridization probes or primers as described herein (*e.g.*, labeled probes or primers), reagents for detection of labeled molecules, restriction enzymes (*e.g.*, for RFLP analysis), allele-specific oligonucleotides, antibodies which bind to altered or to non-altered (native) FLAP polypeptide, means for amplification of nucleic acids comprising a FLAP, or means for analyzing the nucleic acid sequence of a nucleic acid described herein, or for analyzing the amino acid sequence of a polypeptide as described herein, etc. In one embodiment, a kit for diagnosing MI or susceptibility to MI can comprise primers for nucleic acid amplification of a region in the FLAP nucleic acid comprising an at-risk haplotype that is more frequently present in an individual having MI or susceptible to MI. The primers can be designed using portions of the nucleic acids flanking SNPs that are indicative of MI. In a particularly preferred embodiment, the primers are designed to amplify regions of the FLAP nucleic acid associated with an at-risk haplotype for MI, or more particularly the haplotypes defined by the following SNPs: DG00AAFIU, SG13S25, DG00AAJFF,

DG00AAHII, DG00AAHID, B_SNP_310657, SG13S30, SG13S32, SG13S42, and SG13S35 , at the locus on chromosome 13q12.

SCREENING ASSAYS AND AGENTS IDENTIFIED THERBY

The invention provides methods (also referred to herein as "screening assays") for identifying the presence of a nucleotide that hybridizes to a nucleic acid of the invention, as well as for identifying the presence of a polypeptide encoded by a nucleic acid of the invention. In one embodiment, the presence (or absence) of a nucleic acid molecule of interest (*e.g.*, a nucleic acid that has significant homology with a nucleic acid of the invention) in a sample can be assessed by contacting the sample with a nucleic acid comprising a nucleic acid of the invention (*e.g.*, a nucleic acid having the sequence of one of SEQ ID NOs: 1or 3 or the complement thereof, or a nucleic acid encoding an amino acid having the sequence of SEQ ID NO: 2, or a fragment or variant of such nucleic acids), under stringent conditions as described above, and then assessing the sample for the presence (or absence) of hybridization. In a preferred embodiment, high stringency conditions are conditions appropriate for selective hybridization. In another embodiment, a sample containing a nucleic acid molecule of interest is contacted with a nucleic acid containing a contiguous nucleic acid sequence (*e.g.*, a primer or a probe as described above) that is at least partially complementary to a part of the nucleic acid molecule of interest (*e.g.*, a FLAP nucleic acid), and the contacted sample is assessed for the presence or absence of hybridization. In a preferred embodiment, the nucleic acid containing a contiguous nucleic acid sequence is completely complementary to a part of the nucleic acid molecule of interest.

In any of these embodiments, all or a portion of the nucleic acid of interest can be subjected to amplification prior to performing the hybridization.

In another embodiment, the presence (or absence) of a polypeptide of interest, such as a polypeptide of the invention or a fragment or variant thereof, in a sample can be assessed by contacting the sample with an antibody that specifically hybridizes to the polypeptide of interest (*e.g.*, an antibody such as those described above), and

then assessing the sample for the presence (or absence) of binding of the antibody to the polypeptide of interest.

In another embodiment, the invention provides methods for identifying agents (*e.g.*, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes which alter (*e.g.*, increase or decrease) the activity of the polypeptides described herein, or which otherwise interact with the polypeptides herein. For example, such agents can be agents which bind to polypeptides described herein (*e.g.*, binding agent for members of the leukotriene pathway, such as FLAP binding agents); which have a stimulatory or inhibitory effect on, for example, activity of polypeptides of the invention; or which change (*e.g.*, enhance or inhibit) the ability of the polypeptides of the invention to interact with members of the leukotriene pathway binding agents (*e.g.*, receptors or other binding agents); or which alter posttranslational processing of the leukotriene pathway member polypeptide, such as a FLAP polypeptide (*e.g.*, agents that alter proteolytic processing to direct the polypeptide from where it is normally synthesized to another location in the cell, such as the cell surface; agents that alter proteolytic processing such that more polypeptide is released from the cell, etc.)

In one embodiment, the invention provides assays for screening candidate or test agents that bind to or modulate the activity of polypeptides described herein (or biologically active portion(s) thereof), as well as agents identifiable by the assays. Test agents can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to polypeptide libraries, while the other four approaches are applicable to polypeptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S., *Anticancer Drug Des.* 12:145 (1997)).

In one embodiment, to identify agents which alter the activity of a FLAP polypeptide, a cell, cell lysate, or solution containing or expressing a FLAP polypeptide (*e.g.*, SEQ ID NO: 2 or another splicing variant encoded by a FLAP

nucleic acid, such as a nucleic acid comprising a SNP as shown in Table 3), or a fragment or derivative thereof (as described above), can be contacted with an agent to be tested; alternatively, the polypeptide can be contacted directly with the agent to be tested. The level (amount) of FLAP activity is assessed (*e.g.*, the level (amount) of FLAP activity is measured, either directly or indirectly), and is compared with the level of activity in a control (*i.e.*, the level of activity of the FLAP polypeptide or active fragment or derivative thereof in the absence of the agent to be tested). If the level of the activity in the presence of the agent differs, by an amount that is statistically significant, from the level of the activity in the absence of the agent, then the agent is an agent that alters the activity of a FLAP polypeptide. An increase in the level of FLAP activity in the presence of the agent relative to the activity in the absence of the agent, indicates that the agent is an agent that enhances (is an agonist of) FLAP activity. Similarly, a decrease in the level of FLAP activity in the presence of the agent, relative to the activity in the absence of the agent, indicates that the agent is an agent that inhibits (is an antagonist of) FLAP activity. In another embodiment, the level of activity of a FLAP polypeptide or derivative or fragment thereof in the presence of the agent to be tested, is compared with a control level that has previously been established. A statistically significant difference in the level of the activity in the presence of the agent from the control level indicates that the agent alters FLAP activity.

The present invention also relates to an assay for identifying agents which alter the expression of a FLAP nucleic acid (*e.g.*, antisense nucleic acids, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes; which alter (*e.g.*, increase or decrease) expression (*e.g.*, transcription or translation) of the nucleic acid or which otherwise interact with the nucleic acids described herein, as well as agents identifiable by the assays. For example, a solution containing a nucleic acid encoding a FLAP polypeptide (*e.g.*, a FLAP nucleic acid) can be contacted with an agent to be tested. The solution can comprise, for example, cells containing the nucleic acid or cell lysate containing the nucleic acid; alternatively, the solution can be another solution that comprises elements necessary for transcription/translation of the nucleic

acid. Cells not suspended in solution can also be employed, if desired. The level and/or pattern of FLAP expression (*e.g.*, the level and/or pattern of mRNA or of protein expressed, such as the level and/or pattern of different splicing variants) is assessed, and is compared with the level and/or pattern of expression in a control (*i.e.*, the level and/or pattern of the FLAP expression in the absence of the agent to be tested). If the level and/or pattern in the presence of the agent differ, by an amount or in a manner that is statistically significant, from the level and/or pattern in the absence of the agent, then the agent is an agent that alters the expression of the FLAP nucleic acid. Enhancement of FLAP expression indicates that the agent is an agonist of FLAP activity. Similarly, inhibition of FLAP expression indicates that the agent is an antagonist of FLAP activity.

In another embodiment, the level and/or pattern of FLAP polypeptide(s) (*e.g.*, different splicing variants) in the presence of the agent to be tested, is compared with a control level and/or pattern that have previously been established. A level and/or pattern in the presence of the agent that differs from the control level and/or pattern by an amount or in a manner that is statistically significant indicates that the agent alters FLAP expression.

In another embodiment of the invention, agents which alter the expression of a FLAP nucleic acid or which otherwise interact with the nucleic acids described herein, can be identified using a cell, cell lysate, or solution containing a nucleic acid encoding the promoter region of the FLAP nucleic acid operably linked to a reporter gene. After contact with an agent to be tested, the level of expression of the reporter gene (*e.g.*, the level of mRNA or of protein expressed) is assessed, and is compared with the level of expression in a control (*i.e.*, the level of the expression of the reporter gene in the absence of the agent to be tested). If the level in the presence of the agent differs, by an amount or in a manner that is statistically significant, from the level in the absence of the agent, then the agent is an agent that alters the expression of the FLAP nucleic acid, as indicated by its ability to alter expression of a nucleic acid that is operably linked to the FLAP nucleic acid promoter.

Enhancement of the expression of the reporter indicates that the agent is an agonist of FLAP activity. Similarly, inhibition of the expression of the reporter

indicates that the agent is an antagonist of FLAP activity. In another embodiment, the level of expression of the reporter in the presence of the test agent, is compared with a control level that has previously been established. A level in the presence of the agent that differs from the control level by an amount or in a manner that is statistically significant indicates that the agent alters expression.

Agents which alter the amounts of different splicing variants encoded by a FLAP nucleic acid (*e.g.*, an agent which enhances activity of a first splicing variant, and which inhibits activity of a second splicing variant), as well as agents which are agonists of activity of a first splicing variant and antagonists of activity of a second splicing variant, can easily be identified using these methods described above.

In other embodiments of the invention, assays can be used to assess the impact of a test agent on the activity of a polypeptide relative to a FLAP binding agent. For example, a cell that expresses a compound that interacts with a FLAP nucleic acid (herein referred to as a "FLAP binding agent", which can be a polypeptide or other molecule that interacts with a FLAP nucleic acid, such as a receptor, or another molecule, such as 5-LO) is contacted with a FLAP in the presence of a test agent, and the ability of the test agent to alter the interaction between the FLAP and the FLAP binding agent is determined. Alternatively, a cell lysate or a solution containing the FLAP binding agent, can be used. An agent which binds to the FLAP or the FLAP binding agent can alter the interaction by interfering with, or enhancing the ability of the FLAP to bind to, associate with, or otherwise interact with the FLAP binding agent. Determining the ability of the test agent to bind to a FLAP nucleic acid or a FLAP nucleic acid binding agent can be accomplished, for example, by coupling the test agent with a radioisotope or enzymatic label such that binding of the test agent to the polypeptide can be determined by detecting the labeled with ^{125}I, ^{35}S, ^{14}C or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemmission or by scintillation counting. Alternatively, test agents can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product. It is also within the scope of this invention to determine the ability of a test agent to interact with the polypeptide

without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a test agent with a FLAP or a FLAP binding agent without the labeling of either the test agent, FLAP, or the FLAP binding agent. McConnell, H.M. *et al.*, *Science* 257:1906-1912 (1992). As used herein, a "microphysiometer" (*e.g.*, Cytosensor™) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between ligand and polypeptide.

Thus, these receptors can be used to screen for compounds that are agonists for use in treating a disease or condition associated with FLAP or a susceptibility to a disease or condition associated with FLAP, or antagonists for studying a susceptibility to a disease or condition associated with FLAP (*e.g.*, MI). Drugs can be designed to regulate FLAP activation, that in turn can be used to regulate signaling pathways and transcription events of genes downstream or of proteins or polypeptides interacting with FLAP (*e.g.*, 5-LO).

In another embodiment of the invention, assays can be used to identify polypeptides that interact with one or more FLAP polypeptides, as described herein. For example, a yeast two-hybrid system such as that described by Fields and Song (Fields, S. and Song, O., *Nature* 340:245-246 (1989)) can be used to identify polypeptides that interact with one or more FLAP polypeptides. In such a yeast two-hybrid system, vectors are constructed based on the flexibility of a transcription factor that has two functional domains (a DNA binding domain and a transcription activation domain). If the two domains are separated but fused to two different proteins that interact with one another, transcriptional activation can be achieved, and transcription of specific markers (*e.g.*, nutritional markers such as His and Ade, or color markers such as lacZ) can be used to identify the presence of interaction and transcriptional activation. For example, in the methods of the invention, a first vector is used which includes a nucleic acid encoding a DNA binding domain and also a FLAP polypeptide, splicing variant, or fragment or derivative thereof, and a second vector is used which includes a nucleic acid encoding a transcription activation domain and also a nucleic acid encoding a polypeptide which potentially may interact

with the FLAP polypeptide, splicing variant, or fragment or derivative thereof (*e.g.*, a FLAP polypeptide binding agent or receptor). Incubation of yeast containing the first vector and the second vector under appropriate conditions (*e.g.*, mating conditions such as used in the Matchmaker™ system from Clontech (Palo Alto, California, USA)) allows identification of colonies that express the markers of interest. These colonies can be examined to identify the polypeptide(s) that interact with the FLAP polypeptide or fragment or derivative thereof. Such polypeptides may be useful as agents that alter the activity of expression of a FLAP polypeptide, as described above.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either the FLAP, the FLAP binding agent, or other components of the assay on a solid support, in order to facilitate separation of complexed from uncomplexed forms of one or both of the polypeptides, as well as to accommodate automation of the assay. Binding of a test agent to the polypeptide, or interaction of the polypeptide with a binding agent in the presence and absence of a test agent, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein (*e.g.*, a glutathione-S-transferase fusion protein) can be provided which adds a domain that allows a FLAP nucleic acid or a FLAP binding agent to be bound to a matrix or other solid support.

In another embodiment, modulators of expression of nucleic acid molecules of the invention are identified in a method wherein a cell, cell lysate, or solution containing a nucleic acid encoding a FLAP nucleic acid is contacted with a test agent and the expression of appropriate mRNA or polypeptide (*e.g.*, splicing variant(s)) in the cell, cell lysate, or solution, is determined. The level of expression of appropriate mRNA or polypeptide(s) in the presence of the test agent is compared to the level of expression of mRNA or polypeptide(s) in the absence of the test agent. The test agent can then be identified as a modulator of expression based on this comparison. For example, when expression of mRNA or polypeptide is greater (statistically significantly greater) in the presence of the test agent than in its absence, the test agent is identified as a stimulator or enhancer of the mRNA or polypeptide expression. Alternatively, when expression of the mRNA or polypeptide is less (statistically

significantly less) in the presence of the test agent than in its absence, the test agent is identified as an inhibitor of the mRNA or polypeptide expression. The level of mRNA or polypeptide expression in the cells can be determined by methods described herein for detecting mRNA or polypeptide.

In yet another embodiment, the invention provides methods for identifying agents (*e.g.*, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes) which alter (*e.g.*, increase or decrease) the activity of a member of leukotriene pathway binding agent, such as a FLAP binding agent (*e.g.*, 5-LO), as described herein. For example, such agents can be agents which have a stimulatory or inhibitory effect on, for example, the activity of a member of leukotriene pathway binding agent, such as a FLAP binding agent; which change (*e.g.*, enhance or inhibit) the ability a member of leukotriene pathway binding agents, (*e.g.*, receptors or other binding agents) to interact with the polypeptides of the invention; or which alter posttranslational processing of the member of leukotriene pathway binding agent, (*e.g.*, agents that alter proteolytic processing to direct the member of the leukotriene pathway binding agent from where it is normally synthesized to another location in the cell, such as the cell surface; agents that alter proteolytic processing such that more active binding agent is released from the cell, etc.).

For example, the invention provides assays for screening candidate or test agents that bind to or modulate the activity of a member of the leukotriene pathway (or enzymatically active portion(s) thereof), as well as agents identifiable by the assays. As described above, test agents can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to polypeptide libraries, while the other four approaches are applicable to polypeptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. *Anticancer Drug Des., 12*:145 (1997)).

In one embodiment, to identify agents which alter the activity of a member of the leukotriene pathway (such as a FLAP binding agent), a cell, cell lysate, or solution containing or expressing a binding agent (*e.g.*, 5-LO, or a leukotriene pathway member receptor), or a fragment (*e.g.*, an enzymatically active fragment) or derivative thereof, can be contacted with an agent to be tested; alternatively, the binding agent (or fragment or derivative thereof) can be contacted directly with the agent to be tested. The level (amount) of binding agent activity is assessed (either directly or indirectly), and is compared with the level of activity in a control (*i.e.*, the level of activity in the absence of the agent to be tested). If the level of the activity in the presence of the agent differs, by an amount that is statistically significant, from the level of the activity in the absence of the agent, then the agent is an agent that alters the activity of the member of the leukotriene pathway. An increase in the level of the activity relative to a control, indicates that the agent is an agent that enhances (is an agonist of) the activity. Similarly, a decrease in the level of activity relative to a control, indicates that the agent is an agent that inhibits (is an antagonist of) the activity. In another embodiment, the level of activity in the presence of the agent to be tested, is compared with a control level that has previously been established. A level of the activity in the presence of the agent that differs from the control level by an amount that is statistically significant indicates that the agent alters the activity.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a test agent that is a modulating agent, an antisense nucleic acid molecule, a specific antibody, or a polypeptide-binding agent) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent.

Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein. In addition, an agent identified as described herein can be used to alter activity of a polypeptide

encoded by a FLAP nucleic acid, or to alter expression of a FLAP nucleic acid, by contacting the polypeptide or the nucleic acid (or contacting a cell comprising the polypeptide or the nucleic acid) with the agent identified as described herein.

PHARMACEUTICAL COMPOSITIONS

The present invention also pertains to pharmaceutical compositions comprising nucleic acids described herein, particularly nucleotides encoding the polypeptides described herein; comprising polypeptides described herein (*e.g.*, one or more of SEQ ID NO: 1 or 3 or the complement thereof, and/or comprising other splicing variants encoded by a FLAP nucleic acid; and/or an agent that alters (*e.g.*, enhances or inhibits) FLAP nucleic acid expression or FLAP polypeptide activity as described herein. For instance, a polypeptide, protein (*e.g.*, a FLAP receptor), an agent that alters FLAP nucleic acid expression, or a FLAP nucleic acid binding agent or binding partner, fragment, fusion protein or pro-drug thereof, or a nucleotide or nucleic acid construct (vector) comprising a nucleotide of the present invention, or an agent that alters FLAP polypeptide activity, can be formulated with a physiologically acceptable carrier or excipient to prepare a pharmaceutical composition. The carrier and composition can be sterile. The formulation should suit the mode of administration.

Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (*e.g.*, NaCl), saline, buffered saline, alcohols, glycerol, ethanol, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, dextrose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrolidone, etc., as well as combinations thereof. The pharmaceutical preparations can, if desired, be mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active agents.

The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, polyvinyl pyrollidone, sodium saccharine, cellulose, magnesium carbonate, etc.

Methods of introduction of these compositions include, but are not limited to, intradermal, intramuscular, intraperitoneal, intraocular, intravenous, subcutaneous, topical, oral and intranasal. Other suitable methods of introduction can also include gene therapy (as described below), rechargeable or biodegradable devices, particle acceleration devices ("gene guns") and slow release polymeric devices. The pharmaceutical compositions of this invention can also be administered as part of a combinatorial therapy with other agents.

The composition can be formulated in accordance with the routine procedures as a pharmaceutical composition adapted for administration to human beings. For example, compositions for intravenous administration typically are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the composition is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

For topical application, nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water, can be employed. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments,

powders, enemas, lotions, sols, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, *e.g.*, preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. The agent may be incorporated into a cosmetic formulation. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, *e.g.*, pressurized air.

Agents described herein can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The agents are administered in a therapeutically effective amount. The amount of agents which will be therapeutically effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the symptoms, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use of sale for human administration. The pack or kit can be labeled with information regarding mode of administration, sequence of drug

administration (*e.g.*, separately, sequentially or concurrently), or the like. The pack or kit may also include means for reminding the patient to take the therapy. The pack or kit can be a single unit dosage of the combination therapy or it can be a plurality of unit dosages. In particular, the agents can be separated, mixed together in any combination, present in a single vial or tablet. Agents assembled in a blister pack or other dispensing means is preferred. For the purpose of this invention, unit dosage is intended to mean a dosage that is dependent on the individual pharmacodynamics of each agent and administered in FDA approved dosages in standard time courses.

METHODS OF THERAPY

The present invention also pertains to methods of treatment (prophylactic and/or therapeutic) for MI or a susceptibility to MI, using an MI therapeutic agent. An "MI therapeutic agent" is an agent that alters (*e.g.*, enhances or inhibits) FLAP polypeptide activity and/or FLAP nucleic acid expression, as described herein (*e.g.*, a nucleic acid agonist or antagonist). MI therapeutic agents can alter FLAP polypeptide activity or nucleic acid expression by a variety of means, such as, for example, by providing additional FLAP polypeptide or upregulating the transcription or translation of the FLAP nucleic acid; by altering posttranslational processing of the FLAP polypeptide; by altering transcription of FLAP splicing variants; or by interfering with FLAP polypeptide activity (*e.g.*, by binding to a FLAP polypeptide), or by downregulating the transcription or translation of a FLAP nucleic acid. Representative MI therapeutic agents include the following:

nucleic acids or fragments or derivatives thereof described herein, particularly nucleotides encoding the polypeptides described herein and vectors comprising such nucleic acids (*e.g.*, a gene, nucleic acid, cDNA, and/or mRNA, such as a nucleic acid encoding a member of the leukotriene pathway, such as a FLAP polypeptide or active fragment or derivative thereof, or an oligonucleotide; for example, one of SEQ ID Nos. 1 or 3 or the complement thereof, or a nucleic acid encoding SEQ ID NO: 2, or fragments or derivatives thereof);

polypeptides described herein and/or other splicing variants encoded by a FLAP nucleic acid, or fragments or derivatives thereof);

other polypeptides (*e.g.*, receptors of members of the leukotriene pathway, such as LTB4 receptors, LTC4 receptors, LTD4 receptors, Cys LT1 receptors, Cys LT2 receptors); binding agents of the leukotriene pathway, such as FLAP binding agents (*e.g.*, 5-LO); peptidomimetics; fusion proteins or prodrugs thereof; antibodies (*e.g.*, an antibody to an altered FLAP polypeptide, or an antibody to a non-altered FLAP polypeptide, or an antibody to a particular splicing variant encoded by a FLAP nucleic acid, as described above); ribozymes; other small molecules; and

other agents that alter (*e.g.*, enhance or inhibit) a member of the leukotriene pathway gene expression, such as FLAP nucleic acid expression or polypeptide activity, or that regulate transcription of FLAP splicing variants (*e.g.*, agents that affect which splicing variants are expressed, or that affect the amount of each splicing variant that is expressed.

More than one MI therapeutic agent can be used concurrently, if desired.

An MI nucleic acid therapeutic agent that is a nucleic acid is used in the treatment of a susceptibility to MI. The term, "treatment" as used herein, refers not only to ameliorating symptoms associated with the disease, but also preventing or delaying the onset of the disease, and also lessening the severity or frequency of symptoms of the disease. The therapy is designed to alter (*e.g.*, inhibit or enhance), replace or supplement activity of a FLAP polypeptide in an individual. For example, an MI nucleic acid therapeutic agent can be administered in order to upregulate or increase the expression or availability of the FLAP nucleic acid or of specific splicing variants of FLAP nucleic acid, or, conversely, to downregulate or decrease the expression or availability of the FLAP nucleic acid or specific splicing variants of the

FLAP nucleic acid. Upregulation or increasing expression or availability of a native FLAP nucleic acid or of a particular splicing variant could interfere with or compensate for the expression or activity of a defective nucleic acid or another splicing variant; downregulation or decreasing expression or availability of a native FLAP nucleic acid or of a particular splicing variant could minimize the expression or activity of a defective nucleic acid or the particular splicing variant and thereby minimize the impact of the defective nucleic acid or the particular splicing variant.

The MI therapeutic agent(s) are administered in a therapeutically effective amount (*i.e.*, an amount that is sufficient to treat the disease, such as by ameliorating symptoms associated with the disease, preventing or delaying the onset of the disease, and/or also lessening the severity or frequency of symptoms of the disease). The amount which will be therapeutically effective in the treatment of a particular individual's disorder or condition will depend on the symptoms and severity of the disease, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

In one embodiment, a nucleic acid of the invention (*e.g.*, a nucleic acid encoding a FLAP polypeptide, such as one of SEQ ID NO: 1 or 3 or the complement thereof; or another nucleic acid that encodes a FLAP polypeptide or a splicing variant, derivative or fragment thereof, such as a nucleic acid encoding SEQ ID NO: 2, can be used, either alone or in a pharmaceutical composition as described above. For example, a FLAP nucleic acid or a cDNA encoding a FLAP polypeptide, either by itself or included within a vector, can be introduced into cells (either *in vitro* or *in vivo*) such that the cells produce native FLAP polypeptide. If necessary, cells that have been transformed with the nucleic acid or cDNA or a vector comprising the nucleic acid or cDNA can be introduced (or re-introduced) into an individual affected with the disease. Thus, cells which, in nature, lack native FLAP expression and

activity, or have altered FLAP expression and activity, or have expression of a disease-associated FLAP splicing variant, can be engineered to express the FLAP polypeptide or an active fragment of the FLAP polypeptide (or a different variant of the FLAP polypeptide). In a preferred embodiment, nucleic acid encoding a FLAP polypeptide, or an active fragment or derivative thereof, can be introduced into an expression vector, such as a viral vector, and the vector can be introduced into appropriate cells in an animal. Other nucleic acid transfer systems, including viral and nonviral transfer systems, can be used. Alternatively, nonviral nucleic acid transfer methods, such as calcium phosphate coprecipitation, mechanical techniques (*e.g.*, microinjection); membrane fusion-mediated transfer via liposomes; or direct DNA uptake, can also be used.

Alternatively, in another embodiment of the invention, a nucleic acid of the invention; a nucleic acid complementary to a nucleic acid of the invention; or a portion of such a nucleic acid (*e.g.*, an oligonucleotide as described below), can be used in "antisense" therapy, in which a nucleic acid (*e.g.*, an oligonucleotide) which specifically hybridizes to the mRNA and/or genomic DNA of an MI nucleic acid is administered or generated *in situ*. The antisense nucleic acid that specifically hybridizes to the mRNA and/or DNA inhibits expression of the FLAP polypeptide, *e.g.*, by inhibiting translation and/or transcription. Binding of the antisense nucleic acid can be by conventional base pair complementarity, or, for example, in the case of binding to DNA duplexes, through specific interaction in the major groove of the double helix.

An antisense construct of the present invention can be delivered, for example, as an expression plasmid as described above. When the plasmid is transcribed in the cell, it produces RNA that is complementary to a portion of the mRNA and/or DNA that encodes the FLAP polypeptide. Alternatively, the antisense construct can be an oligonucleotide probe that is generated *ex vivo* and introduced into cells; it then inhibits expression by hybridizing with the mRNA and/or genomic DNA of the FLAP. In one embodiment, the oligonucleotide probes are modified oligonucleotides that are resistant to endogenous nucleases, *e.g.*, exonucleases and/or endonucleases, thereby rendering them stable *in vivo*. Exemplary nucleic acid molecules for use as

antisense oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Pat. Nos. 5,176,996, 5,264,564 and 5,256,775). Additionally, general approaches to constructing oligomers useful in antisense therapy are also described, for example, by Van der Krol *et al.* (*Biotechniques* 6:958-976 (1988)); and Stein *et al.* (*Cancer Res.* 48:2659-2668 (1988)). With respect to antisense DNA, oligodeoxyribonucleotides derived from the translation initiation site are preferred.

To perform antisense therapy, oligonucleotides (mRNA, cDNA or DNA) are designed that are complementary to mRNA encoding the FLAP. The antisense oligonucleotides bind to FLAP mRNA transcripts and prevent translation. Absolute complementarity, although preferred, is not required. A sequence "complementary" to a portion of an RNA, as referred to herein, indicates that a sequence has sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid, as described in detail above. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures.

The oligonucleotides used in antisense therapy can be DNA, RNA, or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotides can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotides can include other appended groups such as peptides (*e.g.* for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, *Proc. Natl. Acad. Sci. USA* 86:6553-6556 (1989); Lemaitre *et al.*, *Proc. Natl. Acad. Sci. USA* 84:648-652 (1987); PCT International Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT International Publication No. WO 89/10134), or hybridization-triggered cleavage

agents (see, *e.g.*, Krol *et al.*, *BioTechniques* 6:958-976 (1988)) or intercalating agents. (See, *e.g.*, Zon, Pharm.Res. 5: 539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule (*e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent).

The antisense molecules are delivered to cells that express FLAP *in vivo*. A number of methods can be used for delivering antisense DNA or RNA to cells; *e.g.*, antisense molecules can be injected directly into the tissue site, or modified antisense molecules, designed to target the desired cells (*e.g.*, antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systematically. Alternatively, in a preferred embodiment, a recombinant DNA construct is utilized in which the antisense oligonucleotide is placed under the control of a strong promoter (*e.g.*, pol III or pol II). The use of such a construct to transfect target cells in the patient results in the transcription of sufficient amounts of single stranded RNAs that will form complementary base pairs with the endogenous FLAP transcripts and thereby prevent translation of the FLAP mRNA. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an antisense RNA. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art and described above. For example, a plasmid, cosmid, YAC or viral vector can be used to prepare the recombinant DNA construct that can be introduced directly into the tissue site. Alternatively, viral vectors can be used which selectively infect the desired tissue, in which case administration may be accomplished by another route (*e.g.*, systemically).

Endogenous FLAP expression can also be reduced by inactivating or "knocking out" FLAP or its promoter using targeted homologous recombination (*e.g.*, see Smithies *et al.*, *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson *et al.*, *Cell* 5:313-321 (1989)). For example, an altered, non-functional FLAP (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous FLAP (either the coding regions or regulatory regions of FLAP) can be used, with or without a selectable marker and/or a negative

selectable marker, to transfect cells that express the FLAP *in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the FLAP. The recombinant DNA constructs can be directly administered or targeted to the required site *in vivo* using appropriate vectors, as described above. Alternatively, expression of non-altered FLAPs can be increased using a similar method: targeted homologous recombination can be used to insert a DNA construct comprising a non-altered functional FLAP, or the complement thereof, or a portion thereof, in place of an altered FLAP in the cell, as described above. In another embodiment, targeted homologous recombination can be used to insert a DNA construct comprising a nucleic acid that encodes an MI polypeptide variant that differs from that present in the cell.

Alternatively, endogenous FLAP expression can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of a FLAP (*i.e.*, the FLAP promoter and/or enhancers) to form triple helical structures that prevent transcription of the FLAP in target cells in the body. (See generally, Helene, C., *Anticancer Drug Des.*, 6(6):569-84 (1991); Helene, C. *et al.*, *Ann. N.Y. Acad. Sci.* 660:27-36 (1992); and Maher, L. J., *Bioassays* 14(12):807-15 (1992)). Likewise, the antisense constructs described herein, by antagonizing the normal biological activity of one of the FLAP proteins, can be used in the manipulation of tissue, *e.g.*, tissue differentiation, both *in vivo* and *for ex vivo* tissue cultures. Furthermore, the anti-sense techniques (*e.g.*, microinjection of antisense molecules, or transfection with plasmids whose transcripts are anti-sense with regard to an MI nucleic acid RNA or nucleic acid sequence) can be used to investigate the role of FLAP in normal cellular function. Such techniques can be utilized in cell culture, but can also be used in the creation of transgenic animals.

In yet another embodiment of the invention, other MI therapeutic agents as described herein can also be used in the treatment or prevention of a susceptibility to a disease or condition associated with FLAP. The therapeutic agents can be delivered in a composition, as described above, or by themselves. They can be administered systemically, or can be targeted to a particular tissue. The therapeutic agents can be produced by a variety of means, including chemical synthesis; recombinant

production; *in vivo* production (*e.g.*, a transgenic animal, such as U.S. Pat. No. 4,873,316 to Meade *et al.*), for example, and can be isolated using standard means such as those described herein.

A combination of any of the above methods of treatment (*e.g.*, administration of non-altered FLAP polypeptide in conjunction with antisense therapy targeting altered FLAP mRNA; administration of a first splicing variant encoded by a FLAP in conjunction with antisense therapy targeting a second splicing encoded by a FLAP) can also be used.

The present invention is now illustrated by the following Exemplification, which is not intended to be limiting in any way.

EXEMPLIFICATION

SUBJECTS AND METHODS

Study population

Patients entering the study were defined from an infarction registry that includes all MIs (over 8,000 patients) in Iceland 1981-2000. This registry is a part of the World Health Organization MONICA Project (The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. *J Clin. Epidemiol.* 1988; 41:105-14). Diagnosis of all patients in the registry follow strict diagnostic rules based on symptoms, electrocardiograms, cardiac enzymes, and necropsy findings.

Blood samples from 1342 MI patients, both cases with a family history and sporadic cases were collected. For each patient that participated, blood was collected from 2 relatives (unaffected or affected). Their genotypes were used to help with construction of haplotypes. In addition, blood samples from 624 unrelated controls were collected.

Linkage analysis

Extended families (pedigrees) by clustering related female MI patients were constructed into families such that each patient is related to at least one other patient within and including six meiotic events. The information regarding the relatedness of patients was obtained from an encrypted genealogy database that covers the entire Icelandic nation (Gulcher *et al., Eur. J. Hum. Genet.* 8: 739-742 (2000)). A genomewide scan was performed using a framework map of 1000 microsatellite markers, using protocols described elsewhere (Gretarsdottir S., *et al. Am. J. Hum. Genet.*, 70: 593-603, 2002)). The marker order and positions where obtained from a modified version of the Marshfield genetic map (Center for Medical Genetics, Marshfield Medical Research Foundation), using genetic mapping based on our own data, and from deCODE genetic's high resolution genetic map (Kong A., *et al., Nat. genet.,* 31: 241-247 (2002)). The population-based allele frequencies were constructed from a cohort of more than 30,000 Icelanders who have participated in genetic studies of various disease projects. Additional markers were genotyped within the locus on chromosome 13 to increase the information on identity by descent within the families. For those markers at least 180 Icelandic controls were genotyped to derive the population allele frequencies.

For statistical analysis, multipoint, affected only allele-sharing methods were used to assess evidence for linkage. All results, both the LOD and the non-parametric linkage (NPL) score, were obtained using the program ALLEGRO (Gudbjartsson D.F., *et al., Nat Genet.,* 25: 12-13(2000)). The baseline linkage analysis (Gretarsdottir S., *et al., Am. J. Hum. Genet.* 70: 593-603, (2002)) uses the Spairs scoring function (Whittermore AS, and Haplern J A., *Biometrics* 50: 118-127 (1994)) and Kruglyak *et al., Am. J. Hum. Genet.,* 58:1347-1363 (1996)) the exponential allele-sharing model (Kong A., and Cox N.J., *Am. J. Hum. Genet.* 61:1179-1188 (1997)), and a family weighting scheme which is halfway, on the log-scale, between weighing each affected pairs equally and weighing each family equally.

Ultra-fine mapping and haplotype analysis

A candidate susceptibility locus was defined as the region under the LOD score curve where the score was one lower than the highest lod score ((peak lod score −1)\one lod drop). This region (approx. 12Mb) was ultra-finemapped with microsatellite markers with an average spacing between markers of less than 100kb. All usable microsatellite markers that found in public databases and mapped within that region were used. In addition, microsatellite markers identified within the deCODE genetics sequence assembly of the human genome were used.

Haplotype analysis

The frequencies of haplotypes in the patient and the control groups using an expectation-maximization algorithm were estimated (Dempster A.P. *et al., J. R. Stat. Soc. B.* 39: 1-389 (1977)). An implementation of this algorithm that can handle missing genotypes and uncertainty with the phase was used. Under the null hypothesis, the patients and the controls are assumed to have identical frequencies. Using a likelihood approach, an alternative hypothesis where a candidate at-risk-haplotype is allowed to have a higher frequency in patients than controls, while the ratios of the frequencies of other haplotypes are assumed to be the same in both groups was tested. Likelihoods are maximized separately under both hypothesis and a corresponding 1-df likelihood ratio statistics is used to evaluate the statistic significance.

To look for at-risk-haplotypes in the 1-lod drop, association of all possible combinations of genotyped markers was studied, provided those markers spanned a region of size less than 1000 kb. Due to a certain amount of testing, the *p*-values were adjusted using simulations. The combined patient and control groups were randomly divided into two sets, equal in size to the original group of patients and controls. The haplotype analysis was then repeated and the most significant *p*-value registered was observed. This randomisation scheme was repeated over 100 times to construct an empirical distribution of *p*-values.

SNP haplotype association to MI

In an effort to identify SNP haplotypes that associate with MI we have typed SNPs identified mainly by sequencing the FLAP gene and the region flanking the gene. We genotyped a total number of 45 SNPs in 1343 patients and 624 unrelated controls. The largest subset of unrelated patients (related no closer than 4 meioses) was 921. We observed two correlated series of SNP haplotypes in excess in patients, denoted as A and B in Table 7. The length of the haplotypes varies between 33 and 69 Kb and cover one or two blocks of linkage disequilibrium. Both series of haplotypes contain the common allele 2 of the SNP SG13S25. All haplotypes in the A series contain the SNP DG00AAHID, while all haplotypes in the B series contain the SNP DG00AAHII. In the B series, the haplotypes B4, B5, and B6 have a relative risk (RR) greater than 2 and allelic frequencies above 10% (Table 1). The haplotypes in the A series have slightly lower RR and p-values, but higher allelic frequency (15-16%), and as such we also consider them interesting. The haplotypes in series B and A are strongly correlated, *i.e.* the B haplotypes define a subset of the A haplotypes. Hence, B haplotypes are more specific than A haplotypes. However, A haplotypes are more sensitive, *i.e.* they capture more individuals with the putative mutation, as is observed in the population attributable risk which is less for B than for A. Furthermore, these haplotypes show similar risk ratios and allelic frequency for early-onset patients (defined as onset of first MI before the age of 55). In addition, analyzing various groups of patients with known risk factors, such as hypertension, high cholesterol, smoking and diabetes, did not reveal any significant correlation with these haplotypes.

In conclusion, we have identified a series of correlated MI disease risk haplotypes, consisting of 4-6 SNPs, with relative risk greater than 2 and allelic frequency in MI patients greater than 10%. The length of the haplotypes varies between 39-68 kb. These haplotypes are carried by 19% (B5) to 29% (A4) of MI patients. Our results suggest that the 'at risk' haplotypes in the FLAP gene represent a new major independent risk factor for MI.

Discussion

In a genome wide search for susceptibility nucleic acids for MI, a locus to 13q12 was mapped. This locus was ultra-fine mapped with microsatellite markers. Haplotype analysis strongly suggested a nucleic acid for FLAP (ALOX5AP), as a susceptibility gene for MI.

The FLAP gene encodes for a protein that is required for leukotriene synthesis (LTA4, LTB4, LTC4, LTD4). Inhibitors of its function impede translocation of 5-lipoxygenase from the cytoplasm to the cell membrane and inhibit activation of 5-lipoxygenase. The leukotrienes are potent inflammatory lipid mediators derived from arachidonic acid that can potentially contribute to development of atherosclerosis and destabilization of atherosclerotic plaques through lipid oxidation and/or proinflammatory effects. Allen *et al.,* (*Circulation.* 97: 2406-2413(1998)) described a novel mechanism in which atherosclerosis is associated with the appearance of a leukotriene receptor(s) capable of inducing hyperreactivity of human epicardial coronary arteries in response to LTC4 and LTD4. Allen *et al.* show a photomicrograph of a section of human atherosclerotic coronary artery a positive staining of a number of members of the leukotriene pathway, including FLAP. Mehrabian *et al.* described the identification of 5-Lipoxygenase (5-LO) as a major gene contributing to atherosclerosis susceptibility in mice. Mehrabian *et al.* described that heterozygous deficiency for the enzyme in a knockout model decreased the atherosclerotic lesion size in LDL-/- mice by about 95%. Mehrabian *et al* show that the enzyme is expressed abundantly in macrophage-rich regions of atherosclerotic lesions, and suggested that 5-LO and/or its products might act locally to promote lesion development (Mehrabian *et al.*, Circulation Research. 91:120 (2002)).

Studies of FLAP inhibition in animal models of atheroscerosis are scarce. However, in a rabbit model of acute MI assesssed 72 hours after coronary artery ligation the FLAP-inhibitor BAYx1005 madedly reduced mortality, from 65% to 25%, and blocked the increase in CPK and neutrophil accumulation as well as the ECG-changes observed in sham treated animals (*J. Pharmacol. Exp. Ther.,* 276:332 (1996)).

Mutations and /or polymorphisms within the FLAP nucleic acid, and other members of the same pathway (*i.e.*, 5-lipoxygenase, LTA4, LTB4, LTC4, and CysLT2 receptor), that show association with the disease, can be used as a diagnostic test. The members of the 5-LO pathway in particular are valuable therapeutic targets for myocardial infarction.

Table 1 The marker map for chromosome 13 used in the linkage analysis.

Location (cM)	**Marker**	**Location (cM)**	**Marker**
6	D13S175	63.9	D13S170
9.8	D13S1243	68.7	D13S265
13.5	D13S1304	73	D13S167
17.2	D13S217	76.3	D13S1241
21.5	D13S289	79.5	D13S1298
25.1	D13S171	81.6	D13S1267
28.9	D13S219	84.7	D13S1256
32.9	D13S218	85.1	D13S158
38.3	D13S263	87	D13S274
42.8	D13S326	93.5	D13S173
45.6	D13S153	96.7	D13S778
49.4	D13S1320	102.7	D13S1315
52.6	D13S1296	110.6	D13S285
55.9	D13S156	115	D13S293
59.8	D13S1306		

Table 2 Marker Map for the second step of Linkage Analysis

Location (cM)	Marker	Location (cM)	Marker
1.758	D13S175	42.585	D13S1248
9.235	D13S787	44.288	D13S1233
11.565	D13S1243	44.377	D13S263
16.898	D13S221	45.535	D13S325
17.454	D13S1304	45.536	D13S1270
18.011	D13S1254	45.537	D13S1276
18.59	D13S625	49.149	D13S326
19.308	D13S1244	49.532	D13S1272
19.768	D13S243	52.421	D13S168
22.234	D13S1250	52.674	D13S287
22.642	D13S1242	60.536	D13S1320
22.879	D13S217	64.272	D13S1296
25.013	D13S1299	71.287	D13S156
28.136	D13S289	76.828	D13S1306
28.678	D13S290	77.86	D13S170
29.134	D13S1287	82.828	D13S265
30.073	D13S260	91.199	D13S1241
31.98	D13S171	93.863	D13S1298
32.859	D13S267	97.735	D13S779
33.069	D13S1293	100.547	D13S1256
33.07	D13S620	102.277	D13S274
34.131	D13S220	111.885	D13S173
36.427	D13S219	112.198	D13S796
39.458	D13S1808	115.619	D13S778
40.441	D13S218	119.036	D13S1315
41.113	D13S1288	126.898	D13S285
41.996	D13S1253	131.962	D13S293

Table 3 shows the five exons with positions that encode the FLAP protein, markers and SNPs identified within the genomic sequence by the methods described herein. Of the six SNPs, one SNP, B_SNP_302465, is in the coding region. The polymorphism, SNP 302465, does not change the amino acid sequence in the protein.

Table 3

Exons/markers/SNPs	Position(bp)	Size(bp)	SNPs
D13S289	249198-249445	248	
DG13S166	249855-250249	395	
Exon1	293667-293736	70	
Exon2	302413-302512	100	
B_SNP_302465	**302465**	**1**	heterozygous C-T (3%)
B_SNP_302524	302524	1	heterozygous A-C (55%)
			homozygous A-A (22.5%)
			homozygous C-C (22.5%)
B_SNP_302560	302560	1	heterozygous A-G (2%)
B_SNP_302617	302617	1	heterozygous C-T (37%)
			homozygous T-T (59%)
			homozygous C-C (4%)
Exon3	310405-310475	71	
B_SNP_310657	310657	1	heteroygous A-G (6%)
Exon4	314297-314378	82	
B_SNP_314500	314500	1	heterozygous G-C (24%)
			homozygous C-C (6%)
			Homozygous G-G (70%)
Exon5	322297-322459	163	
DG13S164	330669-330886	218	
D13S1238	330679-330831	153	

DG13S163	363743-363904	162	
SNP13B_R1028729 (rs1028729)	145600	1	homozygousC-C (11%),
			heterozygous C-T(41%)
			homozygous T-T (47%)
SNP13B_Y1323898 (rs1323898)*	151047	1	homozygousG-G(38%)
			heterozygous G-A(47%)
			homozygous A-A (15%)
SNP13B_K912392 (rs912392)*	193119	1	homozygousC-C (13%)
			heterozygous C-T(46%)
			homozygous T-T (41%)
DG00AAFQR (rs1556428)*	117676	1	homozygousG-G(1%)
			heterozygous G-A(18%)
			homozygous A-A (80%)
DG00AAFIV (rs22485654)*	227629	1	homozygousT-T (75%)
			heterozygous T-A(23%)
			homozygous A-A (2%)
DG00AFJT	293754	1	HomozygousC-C (45%),
			heterozygous C-A(45%),
			homozygous A-A (10%)
DG00AAHII	294503	1	homozygousG-G (44%),
			heterozygous G-A(46%),
			homozygous A-A (10%)
DG00AAHID	296020	1	homozygousT-T (43%),
			heterozygous T-A(45%),
			homozygous A-A (12%)
DG00AAHIJ	298098	1	homozygousG-G(60%),
			heterozygous G-A(35%),
			homozygous A-A (6%)
DG00AAHIH	298188	1	homozygousG-G(32%),
			heterozygous G-A(48%),
			homozygous A-A (19%)

DG00AAHIE (rs3885907)*	298379	1	homozygous C-C (23%),
			heterozygous C-A(48%),
			homozygous A-A (29%)
DG00AAHIG	304334	1	homozygousC-C (21%),
			heterozygous C-T(49%),
			homozygous T-T (31%)
DG00AAHIF	324849	1	homozygousG-G (54%),
			heterozygous G-C(39%),
			homozygous C-C (7%)
DG00AAHOI	325651	1	homozygousG-G (59%),
			heterozygous G-A(36%),
			homozygous A-A (5%)
FLA267479	267479	1	
FLA267696	267696	1	
FLA267853	267853	1	
FLA270742	270742	1	
FLA270830	270830	1	
FLA273407	273407	1	
FLA274084	274084	1	
FLA275784	275784	1	
FLA275952	275952	1	
FLA277478	277478	1	
FLA277678	277678	1	
FLA278185	278185	1	
FLA278492	278492	1	
FLA278845	278845	1	
FLA280183	280183	1	
FLA280923	280923	1	
FLA283400	283400	1	
FLA283477/SG13S25	283477	1	
FLA284410	284410	1	
FLA284815	284815	1	
FLA284903	284903	1	
FLA290195	290195	1	
FLA290553	290553	1	
FLA290570	290570	1	
FLA292253	292253	1	
FLA292576	292576	1	
FLA295036	295036	1	
FLA296102	296102	1	

FLA298098	298098	1	
FLA298188	298188	1	
FLA298230	298230	1	
FLA298379	298379	1	
FLA298507	298507	1	
FLA298604	298604	1	
FLA298987	298987	1	
FLA299063	299063	1	
FLA299772	299772	1	
FLA299843	299843	1	
FLA299980	299980	1	
FLA300662	300662	1	
FLA300864	300864	1	
FLA302094	302094	1	
FLA302465	302465	1	
FLA302524	302524	1	
FLA303769	303769	1	
FLA303796	303796	1	
FLA303957	303957	1	
FLA303967	303967	1	
FLA304170	304170	1	
FLA304334	304334	1	
FLA304512	304512	1	
FLA304583	304583	1	
FLA305089	305089	1	
FLA305505	305505	1	
FLA305678	305678	1	
FLA305956	305956	1	
FLA306447	306447	1	
FLA307155	307155	1	
FLA307165	307165	1	
FLA308514	308514	1	
FLA308527	308527	1	
FLA309851	309851	1	
FLA310657	310657	1	
FLA311122	311122	1	
FLA311248	311248	1	
FLA311737	311737	1	
FLA312038	312038	1	
FLA312056/SG13S30	312056	1	
FLA314500	314500	1	
FLA314532	314532	1	
FLA315014	315014	1	
FLA315232	315232	1	
FLA315355	315355	1	

FLA315611	315611	1	
FLA316131	316131	1	
FLA316408	316408	1	
FLA316472	316472	1	
FLA316515	316515	1	
FLA316569	316569	1	
FLA316607	316607	1	
FLA316763/SG13S32	316763	1	
FLA317496	317496	1	
FLA317619	317619	1	
FLA317620	317620	1	
FLA317647	317647	1	
FLA317733	317733	1	
FLA317744	317744	1	
FLA317815	317815	1	
FLA318219	318219	1	
FLA319969	319969	1	
FLA320261	320261	1	
FLA320393/SG13S42	320393	1	
FLA320595	320595	1	
FLA321774	321774	1	
FLA321966	321966	1	
FLA322025	322025	1	
FLA322093	322093	1	
FLA323013	323013	1	
FLA323316/SG13S34	323316	1	
FLA323366	323366	1	
FLA324591	324591	1	
FLA324601	324601	1	
FLA324849	324849	1	
FLA325369	325369	1	
FLA326187	326187	1	
FLA326657	326657	1	
FLA327265	327265	1	
FLA328964	328964	1	
FLA330265	330265	1	
FLA330455	330455	1	
FLA331234	331234	1	
FLA331374	331374	1	
FLA331395	331395	1	
FLA331473	331473	1	
FLA331517	331517	1	
FLA331526	331526	1	
FLA331651	331651	1	
FLA331841	331841	1	

FLA287889/DG00AAJFF	287889	1	
DG00AAFIU/SNP_13_Y1323892	256047	1	
SG13S35/FLA324333	324333	1	
SG13S86	305031	1	
* indicates a publicly available SNP.			

Table 4

Most significant 4 microsatellite marker haplotypes. Length=length of haplotype in Mb. P-val=p-value. RR=Relative risk. N af=Number of patients. P al=allelic frequency of haplotype. P ca =carrier frequency of haplotype. N ct= number of controls. Alleles= alleles in the haplotype. Markers= markers in the haplotype.

4 markers:		pos.rr-frqgt1perc											
length	p-val	RR	N_af	P_al	P_ca	N_ct	P_al	P_ca	Alleles				Markers
0.88	4.71E-06	6.23	428	0.065	0.125	721	0.011	0.022	0	-12	-6	0	DG13S80 DG13S83 DG13S1110 DG13S163
0.82	8.60E-06	INF	438	0.032	0.062	720	0	0	0	4	2	14	DG13S1111 DG13S1103 D13S1287 DG13S1061
0.67	6.98E-06	19.91	435	0.03	0.059	721	0.002	0.003	8	6	0	8	DG13S1103 DG13S163 D13S290 DG13S1061
0.767	4.85E-06	26.72	436	0.048	0.094	721	0.002	0.004	0	0	2	12	DG13S1101 DG13S166 D13S1287 DG13S1061
0.515	1.93E-06	INF	422	0.048	0.094	721	0	0	2	0	0	6	DG13S166 DG13S163 D13S290 DG13S1061
0.864	1.68E-06	INF	424	0.024	0.048	717	0	0	0	2	0	16	DG13S166 DG13S163 -DG13S1061 DG13S293
0.927	5.38E-06	INF	435	0.034	0.067	720	0	0	4	2	14	3	DG13S1103 D13S1287 DG13S1061 DG13S301

Table 5

Most significant 5 microsatellite marker haplotypes. Length=length of haplotype in Mb. P-val=p-value. RR=Relative risk. N af=Number of patients. P al=allelic frequency of haplotype. P ca =carrier frequency of haplotype. N ct= number of controls. Alleles= alleles in the haplotype. Markers= markers in the haplotype

5markers	:	pos.rr-frqgt1perc												
length	p-val	RR	N_af	P_al	P_ca	N_ct	P_al	P_ca	Alleles					Markers
0.851	7.45E-06	15.43	413	0.034	0.067	715	0.002	0.005	0	18	0	0	0	DG13S79 D13S1299 DG13S87 D13S1246 DG13S166
0.964	8.07E-06	INF	437	0.023	0.045	721	0	0	0	-12	6	8	6	DG13S79 DG13S83 DG13S1104 DG13S1103 DG13S163
0.964	2.38E-06	INF	437	0.026	0.052	720	0	0	0	6	0	8	6	DG13S79 DG13S1104 DG13S172 DG13S1103 DG13S163
0.931	7.05E-06	5.8	429	0.068	0.131	721	0.012	0.025	0	-6	0	0	-2	DG13S79 DG13S1110 DG13S175 DG13S166 D13S1238
0.964	8.13E-06	INF	434	0.021	0.041	721	0	0	0	3	8	2	6	DG13S79 DG13S1098 DG13S1103 DG13S166 DG13S163
0.597	9.78E-06	4.58	428	0.074	0.143	717	0.017	0.034	-6	0	0	0	-2	DG13S1110 DG13S89 DG13S175 DG13S166 D13S1238
0.896	6.92E-06	INF	428	0.026	0.051	721	0	0	-12	-6	0	-2	2	DG13S83 DG13S1110 DG13S166 D13S1238 D13S290
0.722	2.18E-06	INF	453	0.026	0.051	738	0	0	-6	0	0	-2	2	DG13S1110 D13S289 DG13S166 D13S1238 D13S290
0.982	7.88E-06	INF	437	0.028	0.055	721	0	0	0	0	4	2	14	DG13S87 DG13S175 DG13S1103 D13S1287 DG13S1061
0.841	8.88E-06	INF	438	0.032	0.062	720	0	0	0	0	4	2	14	DG13S89 DG13S1111 DG13S1103 D13S1287

														DG13S1061
0.841	9.67E-07	INF	435	0.029	0.057	721	0	0	0	8	6	0	8	DG13S89 DG13S1103 DG13S163 D13S290 DG13S1061
0.982	7.90E-06	18.63	437	0.026	0.052	721	0.001	0.003	0	4	0	2	14	DG13S87 DG13S1103 DG13S166 D13S1287 DG13S1061
0.841	3.52E-06	28.52	436	0.048	0.094	721	0.002	0.004	0	0	0	2	12	DG13S89 DG13S1101 DG13S166 D13S1287 DG13S1061
0.705	5.28E-06	INF	435	0.027	0.053	721	0	0	0	8	6	0	8	DG13S175 DG13S1103 DG13S163 D13S290 DG13S1061
0.841	4.21E-06	INF	422	0.048	0.093	721	0	0	0	2	0	0	6	DG13S89 DG13S166 DG13S163 D13S290 DG13S1061
0.767	4.02E-06	28.11	436	0.049	0.095	721	0.002	0.004	0	0	0	2	12	DG13S1101 DG13S175 DG13S166 D13S1287 DG13S1061
0.767	1.29E-06	31.07	436	0.047	0.092	721	0.002	0.003	0	0	0	2	12	DG13S1101 DG13S172 DG13S166 D13S1287 DG13S1061
0.705	4.25E-07	INF	422	0.048	0.093	721	0	0	0	2	0	0	6	DG13S175 DG13S166 DG13S163 D13S290 DG13S1061
0.683	6.58E-06	INF	437	0.029	0.056	721	0	0	0	4	0	2	14	DG13S172 DG13S1103 DG13S166 D13S1287 DG13S1061
0.767	2.85E-06	32.43	436	0.044	0.087	721	0.001	0.003	0	0	0	2	12	DG13S1101 DG13S166 D13S290 D13S1287 DG13S1061
0.865	9.58E-06	18.39	451	0.023	0.045	739	0.001	0.003	0	0	2	2	-16	D13S289 DG13S166 DG13S163 D13S1287 DG13S293
0.865	5.08E-06	INF	453	0.019	0.038	739	0	0	0	0	2	0	-16	D13S289 DG13S166 DG13S163 DG13S1061 DG13S293
0.927	1.02E-07	27.65	437	0.037	0.073	721	0.001	0.003	4	0	2	14	3	DG13S1103 DG13S166 D13S1287 DG13S1061 DG13S301

Table 6

Position (Mb) of microsatellite markers sequence assembly (SA5), primers and size of the markers.

mb	marker	forward	reverse	size
25.09 2042	DG13S2101	ACGGTGATGACGCCTACATT (SEQ ID NO:. 4)	TCACATGGACCAATTACCTAGA A(SEQ ID NO: 5)	188
25.09 2042	DG13S48	CAAATTTCAGATGTGCCAACC (SEQ ID NO: 6)	ACGGTGATGACGCCTACATT(S EQ ID NO: 7)	214
25.39 6504	D13S1304	ACCAGCCTTTGCTTAGGA(SEQ ID NO: 8)	ACATTCTAGTGCTACAGGGTA CTC(SEQ ID NO: 9)	133
25.39 6535	DG13S2105	TGTTCTGCACACGAACATTCT(SE Q ID NO: 10)	TCCTGAGTCCTCTCCACCTG(S EQ ID NO: 11)	104
25.44 5511	DG13S2106	TGGGAATTAATGAAGAACAACAA A(SEQ ID NO: 12)	CATGTTTCGAAGAACTCAAGA GG(SEQ ID NO: 13)	428
25.54 4920	D13S1254	AAATTACTTCATCTTGACGATAAC A(SEQ ID NO: 14)	CTATTGGGGACTGCAGAGAG (SEQ ID NO: 15)	218
25.54 4925	DG13S2107	GGGACTGCAGAGAGCAGAAG (SEQ ID NO: 16)	CAAGAAGGGAAATTCCTACGC (SEQ ID NO: 17)	95
25.56 5956	DG13S55	AGCCAGTGTCCACAAGGAAG (SEQ ID NO: 18)	GAGGGTGAGACACATCTCTGG (SEQ ID NO: 19)	283
25.60 5793	DG13S54	AATCGTGCCTCAGTTCCATC (SEQ ID NO: 20)	CCACCAGGAACAACACACAC (SEQ ID NO: 21)	156
25.61 9693	D13S625	TTGCTCTCCAGCCTGGGC (SEQ ID NO: 22)	TTCCTCTGGCTGCCTGCG (SEQ ID NO: 23)	185
25.68 7422	DG13S1479	TTTGATTCCGTGGTCCATTA (SEQ ID NO: 24)	TTATTTGGTCGGTGCACCTTT (SEQ ID NO.25)	339
25.74 9344	DG13S1440	GGTAGGTTGAAATGGGCTAACA (SEQ ID NO: 26)	TCATGACAAGGTGTTGGATTT (SEQ ID NO: 27)	153
25.90 1212	DG13S1890	CCTCCTCTGCCATGAAGCTA (SEQ ID NO: 28)	CTATTTGGTCTGCGGGTTGT (SEQ ID NO: 29)	418
25.92 8081	DG13S1879	TTTGAGCCCAGATCTAAGCAA (SEQ ID NO: 30)	AAATGTTAATGTCACCGACAAA (SEQ ID NO: 31)	443
25.93 2609	DG13S1540	TACTGGGTTATCGCCTGACC (SEQ ID NO: 32)	CCAATGGACCTCTTGGACAT (SEQ ID NO: 33)	152
25.94 6743	DG13S1889	TTTGAATGTTCATATATTTGTGGT G (SEQ ID NO: 34)	CCCTCGTAATGAAACCTATTTG A (SEQ ID NO: 35)	222
25.94 8679	DG13S59	TTTCGGCACAGTCCTCAATA (SEQ ID NO: 36)	CAGGGTGTGGTGACAT (SEQ ID NO: 37)	228
25.95 2347	DG13S1894	TGTTTCTTTCTTTCTCTCTCTCTT TC (SEQ ID NO: 38)	AAATGAGTTCAATGAGTTGTGG TT (SEQ ID NO: 39)	209
25.98 8360	DG13S1545	CAGAGAGGAACAGGCAGAGG (SEQ ID NO: 40)	AGTGGCTGGGAAGCCTTATT (SEQ ID NO:41)	394
26.07 1866	DG13S1524	AGGTGAGAGAACAAACCTGTCTT (SEQ ID NO: 42)	GCCTTCCTTCTAAGGCCAAC (SEQ ID NO: 43)	115
26.18 3492	DG13S1491	TGTTATACATTTCAATTTCACCTC A (SEQ ID NO: 44)	GTACTCCAGCCGGGCAAC (SEQ ID NO: 45)	286
26.23 6289	DG13S62	TTGTTCAGTGCTCTATAGTTACAA AGT (SEQ ID NO: 46)	GGTCACAAAGCTATGCGATTA (SEQ ID NO: 47)	158
26.27	D13S1244	TCAACAAGTGGATTAAGAAACTG	CTGTTTATGGCTGAGAAGTATG	86

3463		TG (SEQ ID NO: 48)	C (SEQ ID NO:49)	
26.28 6935	DG13S64	TAGCAGGGTGCAGTCTA (SEQ ID NO:50)	ACCATACCACCACCACCATC (SEQ ID NO: 51)	247
26.31 4501	D13S243	ACTGTACTTCTGCCTGGGC (SEQ ID NO: 52)	TTTTGTAATGCCTCAACCATG (SEQ ID NO: 53)	147
26.32 7184	DG13S1529	CTGTAGACTTTATCCCTGACTTA CTG (SEQ ID NO: 54)	CAATGAATGATGAAGATTCCAC TC (SEQ ID NO: 55)	132
26.33 8767	DG13S1908	TGACACCATGTCTTACTGTTTGC (SEQ ID NO: 56)	GAGGATACAATGAGAACCAAA TCTC (SEQ ID NO: 57)	224
26.38 8034	DG13S1546	CCACAGAATGCTCCAAAGGT (SEQ ID NO: 58)	GAGTTCAAGTGATGGATGACG A (SEQ ID NO.59)	357
26.43 5811	DG13S1444	CAGATAGATGAATAGGTGGATGG A (SEQ ID NO: 60)	CACTGTTCCAAGTGCTTTGC (SEQ ID NO: 61)	193
26.48 6657	DG13S1458	GCAGGGCAAACTGCCTTAT (SEQ ID NO:62)	TTTGGTGAAATGTCTGTTTATG G (SEQ ID NO: 63)	402
26.50 4545	D13S252	CTCAACCTGGCTTCTACT (SEQ ID NO: 64)	TACTCCTTAATAAACTCCCC (SEQ ID NO: 65)	338
26.50 8231	DG13S66	TATGCGTTGTGTGTGTG (SEQ ID NO:66)	GGGCCTTAGATTCTTGTAGTG G (SEQ ID NO: 67)	217
27.11 5120	DG13S1554	CTCGCATCTCGCTTCTCACT (SEQ ID NO: 68)	CTCAAGGGTCCAGTGGTTTG (SEQ ID NO: 69)	420
27.14 0675	DG13S1907	TGTCCAGACTGCCTCCTACA (SEQ ID NO:70)	TGCAACACCTGGTTCACAAT (SEQ ID NO: 71)	131
27.14 5842	D13S802	CACAGTGAGACTCTATCTCAAAA A (SEQ ID NO: 72)	TCAGACTGGCTTAGACTGTGG (SEQ ID NO: 73)	150
27.24 0616	DG13S1892	AAATTCCAAAGGCCAGGTG (SEQ ID NO: 74)	CCATACAGTTTCCTAGGTTCTG G (SEQ ID NO: 75)	373
27.25 3452	DG13S1849	CACCTGGCCAAATGTTTGTT (SEQ ID NO: 76)	TGCTTGAATCCAGAGACTGC (SEQ ID NO: 77)	190
27.27 3860	DG13S68	TTTGCGAGTCCTTGTGGAGT (SEQ ID NO: 78)	ACAGTCCGCTCCCTCCTAAT (SEQ ID NO: 79)	238
27.28 0461	DG13S69	ATGCTTGGCCCTCAGTTT (SEQ ID NO: 80)	TTGGCAACCCAAGCTAATATG (SEQ ID NO:81)	296
27.48 3799	D13S1250	CTCCACAGTGACAGTGAGG (SEQ ID NO:82)	GAGAGGTTCCCAATCCC (SEQ ID NO: 83)	160
27.61 0406	D13S1448	CATCAACCTCCCCACCAC (SEQ ID NO: 84)	TATTTTTTCAGTCCCACAGTTA GC (SEQ ID NO:85)	227
27.61 5814	DG13S574	CAGCTCCTGGCCATATTTCT (SEQ ID NO: 86)	GAGCCATTTCTCTGGGTCTG (SEQ ID NO:87)	153
27.64 1211	DG13S73	GGTCCGTGTCAACCCTTAGA (SEQ ID NO: 88)	CAGGTTGATGGGAGGGAAA (SEQ ID NO: 89)	198
27.66 1507	DG13S1532	CGGGAAATGACAGTGAGACC (SEQ ID NO: 90)	TGCCTAGATTCTCCCGTAAG (SEQ ID NO: 91)	163
27.70 5347	D13S1242	GTGCCCAGCCAGATTC (SEQ ID NO: 92)	GCCCCCAGTCAGGTTT (SEQ ID NO: 93)	198
27.88 3872	DG13S576	TTTCTCTCTCCACGGAATGAA (SEQ ID NO:94)	AACCCATTCTCACAGGGTGTA (SEQ ID NO: 95)	199
27.89 7365	DG13S1917	AGGAGTGTGGCAGCTTTGAG (SEQ ID NO: 96)	TGGATTCCCGTGAGTACCAG (SEQ ID NO: 97)	165
27.93 2154	D13S217	ATGCTGGGATCACAGGC (SEQ ID NO: 98)	AACCTGGTGGACTTTTGCT (SEQ ID NO: 99)	170
28.08	DG13S581	AGCATTTCCAATGGTGCTTT	CATGTTGATATGCCTGAAGGA	367

0632		(SEQ ID NO: 100)	(SEQ ID NO:101)	
28.16 5348	DG13S1471	CACTGTCTGCTGCCACTCAT (SEQ ID NO:102)	AGAGATTATGTGATGTACCCTC TCTAT(SEQ ID NO:103)	267
28.30 3252	DG13S583	CAAGCCTGGGACACAGAAAT (SEQ ID NO: 104)	TTTGCAGACACCACAACACA (SEQ ID NO: 105)	264
28.30 3256	D13S120	ATGACCTAGAAATGATACTGGC (SEQ ID NO: 106)	CAGACACCACAACACACATT (SEQ ID NO: 107)	175
28.38 5566	D13S1486	TGGTTTAAAAACCTCATGCC (SEQ ID NO: 108)	ATCCCAAACTCTGTACTTATGT AGG (SEQ ID NO: 109)	151
28.41 5530	DG13S1024	TTTGCACATACACATAAGCGAAC (SEQ ID NO: 110)	CACAAATCCCGTGCACTAAA (SEQ ID NO: 111)	139
28.41 5530	DG13S1510	ATTCCTGGGCTCATGGTACA (SEQ ID NO: 112)	TGCCGTCATCTGCTTTAGAA (SEQ ID NO: 113)	390
28.43 0308	DG13S1495	CCTTGGCTGTTGTGACTGGT (SEQ ID NO:114)	CACTCAGGTGGGAGGATCAC (SEQ ID NO: 115)	285
28.51 7541	DG13S1482	GCTGTTTCCTTGGCTTCTTCT (SEQ ID NO: 116)	CCCATACTTGAGATGACCATG A (SEQ ID NO: 117)	291
28.55 1060	DG13S1845	CACTTTGCCAGTAGCCTTGA (SEQ ID NO:118)	TTGGGAAAGTTAACCCAGAGA (SEQ ID NO: 119)	284
28.63 4903	DG13S1030	TTTGGGAAGAGCCATGAGAC (SEQ ID NO: 120)	CTCTGGGCATTGGAGGATTA (SEQ ID NO: 121)	354
28.63 4903	DG13S1467	TTTGGGAAGAGCCATGAGAC (SEQ ID NO: 122)	AATGCCCATGTGCACTGTAG (SEQ ID NO: 123)	231
28.68 6607	DG13S584	GGGAGACAAGTCAGGTGAGG (SEQ ID NO: 124)	CTGAGTATGGAGTCTTCATCAT TATC (SEQ ID NO: 125)	151
28.79 4032	DG13S1519	TCGTCTCGAAGAAAGAAAGAAGA (SEQ ID NO:126)	CACCATGGGTTAATTGCACA (SEQ ID NO: 127)	286
28.87 6156	DG13S77	TGACGTGGGTTCAGGTTGTA (SEQ ID NO: 128)	AGTGCATTGGTGCCTTCTCT (SEQ ID NO: 129)	220
28.97 0723	DG13S586	GGACTGCCAATTCTACAGCA (SEQ ID NO: 130)	TTTCCATGGGAAATTTGGTC (SEQ ID NO: 131)	151
28.97 5641	DG13S79	TGCTACTAGATTTGACCAACCA (SEQ ID NO: 132)	GACTTGTAAAGGATTTAGTGAT TTCG (SEQ ID NO: 133)	128
29.05 9394	DG13S80	GTGGAAGGCCTCTCTTG (SEQ ID NO: 134)	TGCTTCTTGAGGGAAAGCAT (SEQ ID NO: 135)	233
29.12 6152	DG13S82	CACGTGGTTCACCTCTCTAGG (SEQ ID NO: 136)	TTGGCCACTTATTTGTG (SEQ ID NO: 137)	302
29.15 4691	D13S1299	CGATGAGTGACAGGGCT (SEQ ID NO: 138)	CCTCGTGGGTGGAATAA (SEQ ID NO: 139)	225
29.15 4737	DG13S85	TTGGCCATTAGCAATTAGCA (SEQ ID NO: 140)	CGTGGGTGGAATAAATCAGG (SEQ ID NO: 141)	153
29.15 8462	D13S629	GTTGAGGCAAGAGAATCACT (SEQ ID NO: 142)	GCACATTTACACCAGGGTG (SEQ ID NO.143)	145
29.22 4060	DG13S1934	CCTTCAGAGGATTTCCCTTTC (SEQ ID NO: 144)	CTGGTTTGACTCCAGCTTCA (SEQ ID NO: 145)	431
29.24 5462	DG13S1098	TGTTCAAACCTAAGGTGCTTCA (SEQ ID NO: 146)	GAAACAACAACAACAACAACAA CA (SEQ ID NO: 147)	416
29.25 9840	DG13S1104	CCTGGCACGGAATAGACACT (SEQ ID NO: 148)	GGCCTCCTTTGCTCTGAAG (SEQ ID NO: 149)	378
29.29 4436	DG13S1097	CATCCCTGTGGCTGATTAAGA (SEQ ID NO: 150)	AACAGTTCCAGCCCGTTCTA (SEQ ID NO: 151)	162
29.30	DG13S1110	TTTCAAAGGAATATCCAAGTGC	TGGCGTACCATATAAACAGTTC	265

9700		(SEQ ID NO: 152)	TC (SEQ ID NO: 153)	
29.30 9909	DG13S86	TTTCAAAGGAATATCCAAGTGC (SEQ ID NO: 154)	AAACGTGACACTTCCACACA (SEQ ID NO: 155)	177
29.35 9961	DG13S87	TTCAATGAAGGTGCCGAAGT (SEQ ID NO: 156)	TGTCTATCCCAAAGCAA (SEQ ID NO: 157)	218
29.52 2443	DG13S1111	GCAAGACTCTGTTGAAGAAGAAG A (SEQ ID NO: 158)	TCCCTCTGTTTGAGTTTCTCG (SEQ ID NO: 159)	110
29.57 4665	DG13S1101	AGGCACAGTCGCTCATGTC (SEQ ID NO: 160)	AAACTTTAGCTAATGGTGGTCA AA (SEQ ID NO. 161)	333
29.62 2755	DG13S1106	TGTGATTCCAGGGAGCTATCA (SEQ ID NO. 162)	TAGGTGTGTGGAGGACAGCA (SEQ ID NO. 163)	416
29.65 8910	DG13S172	CCAGTTTCAGTTAGCCAAGTCTG (SEQ ID NO: 164)	GAGAGGGAATGAATGCAGGA (SEQ ID NO: 165)	267
29.66 5709	D13S1246	GAGCATGTGTGACTTTCATATTC AG(SEQ ID NO: 166)	AGTGGCTATTCATTGCTACAG G(SEQ ID NO: 167)	177
29.67 2561	*DG13S1103*	TTGCTGGATGCTGGTTTCTA(SEQ ID NO: 168)	AAAGAGAGAGAGAAAGAGAAA GAAAGA(SEQ ID NO: 169)	264
29.82 5975	D13S289	CTGGTTGAGCGGCATT(SEQ ID NO: 170)	TGCAGCCTGGATGACA(SEQ ID NO: 171)	260
29.82 6631	*DG13S166*	CCTATGGAAGCATAGGGAAGAA(SEQ ID NO: 172)	CCCACTTCTGAGTCTCCTGAT(SEQ ID NO: 173)	395
29.90 6689	DG13S164	GGGATGCAGAAAGGATGTGT(SE Q ID NO: 174)	AAGAATGCTGGCCAACGTAA(S EQ ID NO: 177)	218
29.90 6700	D13S1238	CTCTCAGCAGGCATCCA(SEQ ID NO: 178)	GCCAACGTAATTGACACCA(SE Q ID NO:179)	129
30.03 1378	D13S290	CCTTAGGCCCCATAATCT(SEQ ID NO: 180)	CAAATTCCTCAATTGCAAAAT(S EQ ID NO:181)	176
30.08 6303	D13S1229	GGTCATTCAGGGAGCCATTC(SE Q ID NO: 182)	CCATTATATTTCACCAAGAGGC TGC(SEQ ID NO: 183)	119
30.19 2847	DG13S1460	TGCCTGGTCATCTACCCATT(SEQ ID NO: 184)	TCTACTGCAGCGCTGATCTT(S EQ ID NO: 185)	264
30.21 7670	DG13S1933	CATTTATGAATGGAGGTGAAGC(SEQ ID NO: 186)	ATGGGAGCTCAAAGGGAAAT(S EQ ID NO: 187)	186
30.30 3213	DG13S1448	CAGCAGGAAGATGGACAGGT(SE Q ID NO: 188)	CACACTGCATCACACATACCC(SEQ ID NO: 189)	136
30.31 7871	*D13S1287*	TATGCCAGTATGCCTGCT(SEQ ID NO: 190)	GTCACATCAGTCCATTTGC(SE Q ID NO: 191)	232
30.34 2102	*DG13S1061*	CCAAAGCAAGTAACCTCCTCA(S EQ ID NO: 192)	AAACAATCACTGCCCTCTGG(S EQ ID NO. 193)	227
30.57 1837	DG13S1904	TGATGAAATTGCCTAGTGATGC(S EQ ID NO: 194)	GGATCCAATCGTACGCTACC(S EQ ID NO. 195)	136
30.64 3438	DG13S882	CGAATGGGTGACTAACAGCA(SE Q ID NO: 196)	CTGGAGTGCAGGGACATGA(S EQ ID NO: 197)	378
30.66 5937	DG13S295	AAAGAAATATTCCAAGAAGAAAG AAA(SEQ ID NO: 198)	TTGCACAACTTTGTGTAGAGCA T(SEQ ID NO: 199)	279
30.67 4468	D13S1226	GGGTATGTCTTTATTCTCGGCAG TA(SEQ ID NO: 200)	GTGCATTCACAGACCAGTCATT (SEQ ID NO: 201)	219
30.69 0959	DG13S293	GGGCTTGAAGGCACTAAATGT(S EQ ID NO: 202)	CCAAGCAGTAATTCCTTCCTCA (SEQ ID NO:203)	313
30.71 2468	DG13S1490	ACCTAAACACCACGGACTGG(SE Q ID NO: 204)	CAGGTATCGACATTCTTCCAAA (SEQ ID NO: 205)	418
30.82	DG13S93	TGGGAAGCCAGTAAAGTAGGAA(	AAAGAGACTCCACACATCCATT	190

4483		SEQ ID NO: 206)	T(SEQ ID NO: 207)	
30.82 4859	DG13S94	AGGGCTATTCCTCAAGGTGTT(SEQ ID NO: 208)	TGCTAACACTACCCTCGCAAT(SEQ ID NO: 209)	332
30.92 8429	DG13S1534	GGGCAGGAATCTCTGAAGTG (SEQ ID NO: 210)	CTCCACTGAGAAGCCAAGGA(SEQ ID NO. 211)	382
30.94 0369	DG13S95	AGGCCAAGCTGGTCCATAG(SEQ ID NO: 212)	TCTCTCAAAGCCTCGCTCTC(SEQ ID NO: 213)	126
30.97 0238	DG13S96	CCTTTGAGGCTGGATCTGTT(SEQ ID NO: 214)	TTTCCTTATCATTCATTCCCTCA(SEQ ID NO: 215)	218
31.03 8874	D13S260	AGATATTGTCTCCGTTCCATGA(SEQ ID NO: 216)	CCCAGATATAAGGACCTGGCTA(SEQ ID NO: 217)	163
31.09 2294	DG13S17	TTTAAGCCCTGTGGAATGTATTT(SEQ ID NO: 218)	GACATTGCAGGTCAAGTAGGG (SEQ ID NO: 219)	157
31.20 7844	DG13S306	TGCATAAGGCTGGAGACAGA(SEQ ID NO: 220)	CACAGCAGATGGGAGCAAA(SEQ ID NO:221)	158
31.26 0521	DG13S18	GTGCATGTGCATACCAGACC(SEQ ID NO: 222)	GGCAAGATGACCTCTGGAAA(SEQ ID NO: 223)	319
31.29 9720	DG13S1905	GTCCACTGCAGCACACAGAG(SEQ ID NO: 224)	GCACTGGTAGATACATGCTAACG(SEQ ID NO: 225)	383
31.35 3230	DG13S307	GGGTATCTTGGCCAGGTGT(SEQ ID NO: 226)	TGGCTAAGCACAATCCCTTT(SEQ ID NO: 227)	403
31.35 5135	DG13S1062	TTTGTGTTCCAGGTGAGAATTG(SEQ ID NO: 228)	GAACCATATCCCAAGGCACT(SEQ ID NO: 229)	120
31.41 4329	DG13S1874	AACCCAAATCAACAAACCAGA(SEQ ID NO: 230)	AATGAATTCTGGGTCACATGC(SEQ ID NO: 231)	404
31.42 9562	DG13S1093	TTGTTCCCACATTCATTCTACA(SEQ ID NO: 232)	TTAAACTCGTGGCAAAGACG(SEQ ID NO: 233)	273
31.62 6502	DG13S1059	CACCATGCCTGGCTCTTT(SEQ ID NO: 234)	AACTTCTCCAGTTGTGTGGTTG (SEQ ID NO: 235)	330
31.72 3749	DG13S1086	AGCTGAGCTCATGCCACT(SEQ ID NO: 236)	CAAGACCTTGTGCATTTGGA(SEQ ID NO: 237)	155
31.74 6074	DG13S1515	AGCCAGACATGGTAGTGTGC(SEQ ID NO: 238)	GCAATAACTCACACATCAGCAA (SEQ ID NO:239)	417
31.85 5732	D13S171	CCTACCATTGACACTCTCAG(SEQ ID NO: 240)	TAGGGCCATCCATTCT(SEQ ID NO: 241)	231
31.91 7332	DG13S1092	ACCAAGATATGAAGGCCAAA(SEQ ID NO: 242)	CCTCCAGCTAGAACAATGTGAA(SEQ ID NO: 243)	176
32.00 2852	DG13S1449	TGTCCATAGCTGTAGCCCTGT(SEQ ID NO: 244)	CTCAATGGGCATCTTTAGGC(SEQ ID NO: 245)	279
32.07 2957	DG13S1489	TGTAATTCAACGACTGGTGTCC(SEQ ID NO: 246)	AGCTTCTGATGGTTGCTGGT(SEQ ID NO: 247)	130
32.08 3989	DG13S312	CAAACAAACAAACAAGCAAACC(SEQ ID NO: 248)	TGGACGTTTCTTTCAGTGAGG(SEQ ID NO: 249)	349
32.12 5177	DG13S1511	TGATAACTTACCAGCATGTGAGC (SEQ ID NO: 250)	TCACCTCACCTAAGGATCTGC(SEQ ID NO: 251)	314
32.18 3547	DG13S314	CATGCAATTGCCCAATAGAG(SEQ ID NO: 252)	TTGGGCTTGTCTACCTAGTTCA (SEQ ID NO: 253)	335
32.19 5358	DG13S1090	TGGGTTCCTCATACTGGAGTG(SEQ ID NO: 254)	GCCTGAGCTCCAAGCTCTTT(SEQ ID NO: 255)	169
32.25 1038	DG13S1071	GCTGCACGTATTTGTTGGTG(SEQ ID NO: 256)	AAACAGCAGAAATGGGAACC(SEQ ID NO: 257)	239
32.35	DG13S1068	CCGTGGGCTATCAATTTCTG(SE	AAGATGCAATCTGGTTTCCAA(	238

6895		Q ID NO: 258)	SEQ ID NO: 259)	
32.37 3040	DG13S1077	CCCAAGACTGAGGAGGTCAA(SEQ ID NO: 260)	GCTGACGGAGAGGAAAGAGA(SEQ ID NO: 261)	374
32.42 2780	DG13S1906	TGACAAGGGTGTGGTTATGG (SEQ ID NO: 262)	CCGCACTTTCTCTTCTGGAC (SEQ ID NO:263)	425
32.51 1590	DG13S316	TGAGAAGCCTGGGCATTAAG (SEQ ID NO: 264)	ACAAGCTCATCCAGGGAAAG (SEQ ID NO: 265)	243
32.61 0517	DG13S317	TTGGAAAGGAAGAAAGGAAGG (SEQ ID NO: 266)	TTGAAACCTAAATGCCACCTG (SEQ ID NO:267)	215
32.61 0713	D13S1493	ACCTGTTGTATGGCAGCAGT (SEQ ID NO: 268)	GGTTGACTCTTTCCCCAACT (SEQ ID NO: 269)	248
32.78 9894	DG13S1558	AGAGCTGATCTGGCCGAAG (SEQ ID NO:270)	GGTGGACACAGAATCCACACT (SEQ ID NO: 271)	399
32.86 5950	D13S267	GGCCTGAAAGGTATCCTC (SEQ ID NO:272)	TCCCACCATAAGCACAAG (SEQ ID NO: 273)	160
32.96 1410	DG13S1478	TCAACCTAGGATTGGCATTACA (SEQ ID NO: 274)	TCTAGGATTTGTGCCTTTCCA (SEQ ID NO: 275)	387
33.00 9922	DG13S1513	GACGTCTTAGGATTGACTTCTGC (SEQ ID NO: 276)	CCAAATACACATTCTTAAAGGG AAA (SEQ ID NO: 277)	173
33.12 5696	DG13S1461	GACTGCAGATCGTGGGACTT (SEQ ID NO: 278)	TTCTCCAGAGAAACCAAACCA (SEQ ID NO: 279)	148
33.16 8468	DG13S1551	ATTCGTGCAGCTGTTTCTGC (SEQ ID NO. 280)	GCATGACATTGTAAATGGAGG A (SEQ ID NO:281)	263
33.25 4989	DG13S1884	GGTGGGAATGTGTGACTGAA (SEQ ID NO. 282)	CCAGGTACAACATTCTCCTGAT (SEQ ID NO:283)	123
33.34 0124	D13S1293	TGCAGGTGGGAGTCAA (SEQ ID NO. 284)	AAATAACAAGAAGTGACCTTCC TA (SEQ ID NO: 285)	129
33.34 6908	DG13S326	TGTTCTCCTCACCCTGCTCT (SEQ ID NO: 286)	TTTCAGGCTAGGAAGATCCTTT (SEQ ID NO: 287)	261
33.39 2629	DG13S1518	AAAGGATGCATTCGGTTAGAG (SEQ ID NO: 288)	ACTGTCCTGTGCCTGTGCTT (SEQ ID NO: 289)	375
33.40 5527	DG13S23	CCTGAATAGGTGGAATTAAGATC AA (SEQ ID NO: 290)	TCAAGGAGCATACACACACAC A (SEQ ID NO: 291)	107
33.43 1536	D13S620	GTCCACCTAATGGCTCATTC (SEQ ID NO: 292)	CAAGAAGCACTCATGTTTGTG (SEQ ID NO: 293)	185
33.43 7092	DG13S1866	AGCCTGTGATTGGCTGAGA (SEQ ID NO: 294)	GGCTTACAGCTGCCTCCTTT (SEQ ID NO: 295)	410
33.49 5718	DG13S1927	CCCACAGAGCACTTTGTTAGA (SEQ ID NO: 296)	GCCTCCCTTAAGCTGTTATGC (SEQ ID NO: 297)	401
33.50 3440	DG13S1503	CACTCTTTACTGCCAATCACTCC (SEQ ID NO:298)	GCCGTGTGGGTGTATGAAT (SEQ ID NO: 299)	226
33.56 8100	DG13S332	TTGTACCAGGAACCAAAGACAA (SEQ ID NO: 300)	CACAGACAGAGGCACATTGA (SEQ ID NO: 301)	176
33.67 5841	DG13S333	GCTCTGGTCACTCCTGCTGT (SEQ ID NO: 302)	CATGCCTGGCTGATTGTTT (SEQ ID NO: 303)	446
33.77 1389	D13S220	CCAACATCGGGAACTG (SEQ ID NO: 304)	TGCATTCTTTAAGTCCATGTC (SEQ ID NO: 305)	191
33.81 8041	DG13S1919	CAGCAACTGACAACTCATCCA (SEQ ID NO: 306)	CCTCAATCCTCAGCTCCAAC (SEQ ID NO.307)	255
33.87 3614	DG13S1439	TCCTTCACAGCTTCAAACTCA (SEQ ID NO: 308)	AGTGAGAAGCTTCCATACTGG T (SEQ ID NO: 309)	239
33.90	DG13S335	GCCAACCGTTAGACAAATGA	CTACATGTGCACCACAACACC	201

6065		(SEQ ID NO: 310)	(SEQ ID NO: 311)	
33.92 8653	DG13S340	AGTTTATTGCCGCCGAGAG (SEQ ID NO. 312)	ACCCACCACATTCACAAGC (SEQ ID NO: 313)	373
34.01 9455	DG13S1496	CGATTGCCATGTCTCTTTGA (SEQ ID NO: 314)	GAGATCTGGCCTGGATTTGT (SEQ ID NO: 315)	155
34.03 4089	DG13S342	TGAGGCCAGCCTTACCTCTAT (SEQ ID NO: 316)	CCAGACATGGTGGCTTGT (SEQ ID NO: 317)	366
34.06 1777	DG13S344	GAAGGAAGGAAGGGAAGGAA (SEQ ID NOv 318)	AAGGATGAGAAGAGTCCATGC (SEQ ID NO: 319)	292
34.06 7239	DG13S345	AAATACCCTTTGAACAGACACAC (SEQ ID NO: 320)	TAGCTGAGCATGGTGGTACG (SEQ ID NO: 321)	201
34.07 7874	DG13S346	AAAGACAAGACAGCAATCCAAA (SEQ ID NO: 322)	GCAGAACCCAGGCTACAGAT (SEQ ID NO. 323)	152
34.08 4138	DG13S347	TCATTGTCAGCACAGAATGAACT(SEQ ID NO: 324)	GGAGGGAGGGAAGAAAGAGA (SEQ ID NO: 325)	338
34.08 4326	D13S624	GCAACACAGTGAAAGCCCA(SEQ ID NO: 326)	ACAGGAGCATGCCACCATG(SE Q ID NO: 327)	191
34.15 6075	DG13S339	GGGAAGAGGAGATTGACTTGTT(SEQ ID NO: 328)	GGAACACCATCATTCCAACC(S EQ ID NO: 329)	232
34.19 2478	DG13S1926	TACAAGCTCCACCGTCCTTC(SE Q ID NO: 330)	TGAGTTGCTGCCTCTTCAAA(S EQ ID NO: 331)	261
34.22 0227	DG13S1469	TGCTAATGGGCCAAGGAATA(SE Q ID NO: 332)	GCTAAATGTCCTCATGAATAGC C(SEQ ID NO: 333)	382
34.30 1448	DG13S351	TGTCCTGCAGACAGATGGTC(SE Q ID NO: 334)	CCTCCGGAGTAGCTGGATTA(S EQ ID NO: 335)	294
34.38 7883	DG13S26	GAGACTGGCCCTCATTCTTG(SE Q ID NO: 336)	AAGAAGCCAGAGACAAAGAAA TACA(SEQ ID NO: 337)	330
34.53 5441	DG13S30	CATCTATCTTTGGATTCAGTGGT G(SEQ ID NO: 338)	TGCTCCCAACATCTTACCAG(S EQ ID NO: 339)	388
34.56 5594	DG13S1435	TGTCCTCTGGTCATTTCTATGGT(SEQ ID NO: 340)	CATGAATGAGAAGTGATGAAT GG (SEQ ID NO: 341)	235
34.65 9858	DG13S1446	AACACGGGAAATTCCAACAG(SE Q ID NO: 342)	TGAAGAACTGAAATTGCCAGTA A(SEQ ID NO: 343)	379
34.71 2260	DG13S356	CAGACACTGTAAACTGGCTTCG(SEQ ID NO: 344)	GCCACATTGCTATCAGCGTA(S EQ ID NO: 345)	212
34.73 8756	DG13S357	TGTCATAGGCTTGCGGTATTT(SE Q ID NO: 346)	TTGGTAGGGTCCTTTCCTTT(S EQ ID NO: 347)	202
34.77 0571	DG13S1032	GCCTGCTCACTGTTGTTTGA(SE Q ID NO: 348)	CGGTTATCAGAGACTGGTGGT(SEQ ID NO: 349)	211
34.79 9679	DG13S1557	GGCTTATTTCATGTACGGCTA(SE Q ID NO: 350)	GGTTAAACTCTACTTAGTCCTG ATGC(SEQ ID NO: 351)	158
34.88 2934	DG13S1925	GAACTCTGCAGGCACCTCTT(SE Q ID NO: 352)	CCTGAAGCGCTTGTACTGAA(S EQ ID NO: 353)	456
34.93 2690	DG13S1484	TGTTGCGTACTCAGCCCATA (SEQ ID NO:354)	GACAGGTGTCAAACGGGTCT(S EQ ID NO: 355)	246
34.94 2547	DG13S360	TTGGCTTCTCGCTCTTTCTT(SEQ ID NO: 356)	AGCCATCAGTCACATGCAAA (SEQ ID NO: 357)	350
34.99 8979	DG13S1522	AGATCTCCAGGGCAGAGGAC(SE Q ID NO: 358)	CCTTCCTCCCTCCTTCTCTC(S EQ ID NO: 359)	355
35.07 4962	DG13S1517	CGTCATTGATCCCAATCATCT(SE Q ID NO: 360)	GGCTGATAGCCTCCCTTGTA (SEQ ID NO:361)	235
35.07	DG13S1521	GAGAGAGAGCAGCTTGCATGT(S	GGCTGATAGCCTCCCTTGTA(S	172

4962		EQ ID NO:362)	EQ ID NO:363)	
35.12 6882	DG13S364	ACCTTTCAAGCTTCCGGTTT(SEQ ID NO: 364)	TTCCATCCGTCCATCTATCC(SEQ ID NO: 365)	172
35.32 8663	DG13S1036	TTAAAGTCACTTGTCTGTGGTCA(SEQ ID NO: 366)	TTTGTAGGAATCAAGTCAAATAATGTA(SEQ ID NO: 367)	216
35.33 5364	DG13S367	CAAACATCACACTGGGCAAA(SEQ ID NO: 368)	TGCTTTGGAATCTTTCTTGCT(SEQ ID NO: 369)	301
35.37 1957	DG13S1901	CTGCCAGGATGTCAGCATT(SEQ ID NO: 370)	TCCACACTTTCTCATCACCTAAA(SEQ ID NO: 371)	440
35.42 0295	DG13S1037	CTTTCGGAAGCTTGAGCCTA(SEQ ID NO: 372)	CCCAAGACCACTGCCATATT(SEQ ID NO: 373)	269
35.42 5841	DG13S1854	TGACAGGTTTGGGTATATTGGA(SEQ ID NO: 374)	TGCTTAATGTAGTGGCAGCA(SEQ ID NO: 375)	124
35.50 6053	DG13S1038	TCCTGCCTTTGTGAATTCCT(SEQ ID NO: 376)	GTTGAATGAGGTGGGCATTA(SEQ ID NO: 377)	334
35.54 7210	DG13S1039	CCATTTAATCCTCCAGCCATT(SEQ ID NO: 378)	GCTCCACCTTGTTACCCTGA(SEQ ID NO: 379)	167
35.60 9252	DG13S1840	ACAACCCTGGAATCTGGACT(SEQ ID NO: 380)	GAAGGAAAGGAAAGGAAAGAAA(SEQ ID NO: 381)	217
35.61 9286	DG13S369	TGACAAGACTGAAACTTCATCAG(SEQ ID NO: 382)	GATGCTTGCTTTGGGAGGTA(SEQ ID NO: 383)	257
35.62 7911	D13S305	TTGAGGACCTGTCGTTACG (SEQ ID NO: 384)	TTATAGAGCAGTTAAGGCACA (SEQ ID NO: 385)	394
35.65 6659	DG13S375	TGAGGGTGGTAAGCCCTTATT(SEQ ID NO: 386)	GGAGTTGTGGCCTCTCTCTCT(SEQ ID NO: 387)	192
35.76 0368	D13S219	AAGCAAATATGCAAAATTGC(SEQ ID NO: 388)	TCCTTCTGTTTCTTGACTTAACA (SEQ ID NO: 389)	125
35.82 5852	DG13S378	TGCTAAGAGGGCAGATCTCA(SEQ ID NO: 390)	GGCTCATAGCCAATTTCTCC (SEQ ID NO: 391)	324
35.83 2127	DG13S32	CGGCATTCTCAATAACCTCAA (SEQ ID NO: 392)	TCTTTGATGAGGATCAATTAGTGG (SEQ ID NO: 393)	214
35.87 2936	DG13S1549	ACGCACACACACACACACAC (SEQ ID NO: 394)	TGCCTCTGTAATCCTGTGTAGC (SEQ ID NO:395)	260
35.91 2321	DG13S1473	GCTCTAAGGTGGGTCCCAATA (SEQ ID NO:396)	GGGAATGACAAGATCAGTTTACC (SEQ ID NO: 397)	163

Table 7.

The selected SNP haplotypes and the corresponding p-values, relative risk (RR), number of patients (#aff), allelic frequency in patients (aff.frq.), carrier frequency in patients (carr.frq.),number of controls (#con), allelic frequency in controls (con.frq.), population attributable risk (PAR). The patients used for this analysis were all unrelated within 4 meioses.

	p-val	RR	#aff	aff.frq.	carr.frq.	#con	con.frq.	PAR	DG00AAFIU	SG13S25	DG00AAJFF	DG00AAHII	DG00AAHID	B_SNP_310657	SG13S30	SG13S32	SG13S42	SG13S35
B4	4.8E-05	2.08	903	0.106	0.20	619	0.054	0.11		2		2			2		0	
B5	2.4E-05	2.20	910	0.101	0.19	623	0.049	0.11	3	2		2			2		0	
B6	1.8E-06	2.22	913	0.131	0.24	623	0.063	0.14	3	2	2	2				0		2
A4	5.1E-06	1.81	919	0.159	0.29	623	0.095	0.14		2			3	2		0		
A5	2.6E-06	1.91	920	0.150	0.28	624	0.085	0.14	3	2			3	2		0		

All references cited herein are incorporated by reference in their entirety. While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A method of diagnosing a susceptibility to myocardial infarction in an individual, comprising detecting a polymorphism in a FLAP nucleic acid, wherein the presence of the polymorphism in the nucleic acid is indicative of a susceptibility to myocardial infarction.

2. A method of diagnosing a susceptibility to myocardial infarction, comprising detecting an alteration in the expression or composition of a polypeptide encoded by a FLAP nucleic acid in a test sample, in comparison with the expression or composition of a polypeptide encoded by a FLAP nucleic acid in a control sample, wherein the presence of an alteration in expression or composition of the polypeptide in the test sample is indicative of a susceptibility to myocardial infarction.

3. The method of Claim 1 wherein the polymorphism in the FLAP nucleic acid is indicated by detecting the presence of a haplotype comprising one or more of the markers DG00AAFIU, SG13S25, DG00AAJFF, DG00AAHII, DG00AAHID, B_SNP_310657, SG13S30, SG13S32, SG13S42, and SG13S35 at the 13q12 locus comprising a FLAP nucleic acid.

4. The method of Claim 1 wherein the polymorphism comprises at least one of the polymorphisms as indicated in Table 3.

5. A method of diagnosing myocardial infarction, comprising detecting an alteration in the expression or composition of a polypeptide encoded by a FLAP nucleic acid in a test sample, in comparison with the expression or composition of a polypeptide encoded by a FLAP nucleic acid in a control

sample, wherein the presence of an alteration in expression or composition of the polypeptide in the test sample is indicative of myocardial infarction.

6. An isolated nucleic acid molecule comprising a FLAP nucleic acid, wherein the FLAP nucleic acid has a nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of SEQ ID NO: 1 or SEQ ID NO: 3, wherein the nucleic acid molecule comprises a polymorphism as indicated in Table 3.

7. An isolated nucleic acid molecule having a polymorphism as indicated in Table 3, which hybridizes under high stringency conditions to a nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3, or the complement of SEQ ID NO: 1 or SEQ ID NO: 3.

8. A method for assaying for the presence of a first nucleic acid molecule in a sample, comprising contacting said sample with a second nucleic acid molecule, where the second nucleic acid molecule comprises a nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3, and hybridizes to the first nucleic acid under high stringency conditions.

9. A vector comprising an isolated nucleic acid molecule selected from the group consisting of:

a) a nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3; or
b) complement of a nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3;

wherein the nucleic acid molecule is operably linked to a regulatory sequence.

10. A recombinant host cell comprising the vector of Claim 9.

11. A method for producing a polypeptide encoded by an isolated nucleic acid molecule having a polymorphism as indicated in Table 3, comprising culturing

the recombinant host cell of Claim 10 under conditions suitable for expression of the nucleic acid molecule.

12. A method of assaying for the presence of a polypeptide encoded by an isolated nucleic acid molecule according to Claim 6 in a sample, the method comprising contacting the sample with an antibody which specifically binds to the encoded polypeptide.

13. A method of identifying an agent that alters expression of a FLAP nucleic acid, comprising:

a) contacting a solution containing a nucleic acid comprising the promoter region of the FLAP nucleic acid operably linked to a reporter gene with an agent to be tested;

b) assessing the level of expression of the reporter gene; and

c) comparing the level of expression with a level of expression of the reporter gene in the absence of the agent; wherein if the level of expression of the reporter gene in the presence of the agent differs, by an amount that is statistically significant, from the level of expression in the absence of the agent, then the agent is an agent that alters expression of the FLAP nucleic acid.

14. An agent that alters expression of the FLAP nucleic acid, identifiable according to the method of Claim 13.

15. A method of identifying an agent that alters expression of a FLAP nucleic acid, comprising:

a) contacting a solution containing a nucleic acid of Claim 1 or a derivative or fragment thereof with an agent to be tested;

b) comparing expression with expression of the nucleic acid, derivative or fragment in the absence of the agent;

wherein if expression of the nucleotide, derivative or fragment in the presence of the agent differs, by an amount that is statistically significant, from the expression in the absence of the agent, then the agent is an agent that alters expression of the FLAP nucleic acid.

16. The method of Claim 15, wherein the expression of the nucleotide, derivative or fragment in the presence of the agent comprises expression of one or more splicing variant(s) that differ in kind or in quantity from the expression of one or more splicing variant(s) the absence of the agent.

17. An agent that alters expression of a FLAP nucleic acid, identifiable according to the method of Claim 15.

18. An agent that alters expression of a FLAP nucleic acid, selected from the group consisting of: antisense nucleic acid to a FLAP nucleic acid; a FLAP polypeptide; a FLAP nucleic acid receptor; a FLAP nucleic acid binding agent; a peptidomimetic; a fusion protein; a prodrug thereof; an antibody; and a ribozyme.

19. A method of altering expression of a FLAP nucleic acid, comprising contacting a cell containing a FLAP nucleic acid with an agent of Claim 18.

20. A method of identifying a polypeptide which interacts with a FLAP polypeptide, comprising employing a yeast two-hybrid system using a first vector which comprises a nucleic acid encoding a DNA binding domain and a FLAP polypeptide, splicing variant, or a fragment or derivative thereof, and a second vector which comprises a nucleic acid encoding a transcription activation domain and a nucleic acid encoding a test polypeptide, wherein if transcriptional activation occurs in the yeast two-hybrid system, the test polypeptide is a polypeptide which interacts with a FLAP polypeptide.

21. A transgenic animal comprising a nucleic acid selected from the group consisting of: an exogenous FLAP nucleic acid and a nucleic acid encoding a FLAP polypeptide.

22. A method for assaying a sample for the presence of a FLAP nucleic acid, comprising:

a) contacting said sample with a nucleic acid comprising a contiguous nucleic acid sequence which is at least partially complementary to a part of the sequence of said FLAP nucleic acid under conditions appropriate for hybridization; and

b) assessing whether hybridization has occurred between a FLAP nucleic acid nucleic acid and said nucleic acid comprising a contiguous nucleotide sequence which is at least partially complementary to a part of the sequence of said FLAP nucleic acid;

wherein if hybridization has occurred, a FLAP nucleic acid is present in the nucleic acid.

23. The method of Claim 22, wherein said nucleic acid comprising a contiguous nucleic acid sequence is completely complementary to a part of the sequence of said FLAP nucleic acid.

24. The method of Claim 22, comprising amplification of at least part of said FLAP nucleic acid.

25. The method of Claim 22, wherein said contiguous nucleic acid sequence is 100 or fewer nucleotides in length and is either: a) at least 80% identical to a contiguous sequence of nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3; b) at least 80% identical to the complement of a contiguous sequence of nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3; or c) capable of selectively hybridizing to said FLAP nucleic acid.

26. A reagent for assaying a sample for the presence of a FLAP nucleic acid, said reagent comprising a nucleic acid comprising a contiguous nucleic acid sequence which is at least partially complementary to a part of the nucleic acid sequence of said nucleic acid.

27. The reagent of Claim 26, wherein the nucleic acid comprises a contiguous nucleotide sequence, which is completely complementary to a part of the nucleic acid sequence of said FLAP nucleic acid.

28. A reagent kit for assaying a sample for the presence of a FLAP nucleic acid, comprising in separate containers:

a) one or more labeled nucleic acids comprising a contiguous nucleotide sequence which is at least partially complementary to a part of the nucleic acid sequence of said FLAP nucleic acid; and

b) reagents for detection of said label.

29. The reagent kit of Claim 28, wherein the labeled nucleic acid comprises a contiguous nucleotide sequences which is completely complementary to a part of the nucleic acid sequence of said FLAP nucleic acid.

30. A reagent kit for assaying a sample for the presence of a FLAP nucleic acid, comprising one or more nucleic acids comprising a contiguous nucleic acid sequence which is at least partially complementary to a part of the nucleic acid sequence of said FLAP nucleic acid, and which is capable of acting as a primer for said FLAP nucleic acid when maintained under conditions for primer extension.

31. The use of a nucleic acid which is 100 or fewer nucleotides in length and which is either: a) at least 80% identical to a contiguous sequence of nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3; b) at least 80% identical to

the complement of a contiguous sequence of nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3; or c) capable of selectively hybridizing to said FLAP nucleic acid, for assaying a sample for the presence of a FLAP nucleic acid.

32. The use of a first nucleic acid which is 100 or fewer nucleotides in length and which is either:

a) at least 80% identical to a contiguous sequence of nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3;

b) at least 80% identical to the complement of a contiguous sequence of nucleotides of SEQ ID NO: 1 or SEQ ID NO: 3; or

c) capable of selectively hybridizing to said FLAP nucleic acid; for assaying a sample for the presence of a FLAP nucleic acid that has at least one nucleotide difference from the first nucleic acid.

33. The use of a nucleic acid which is 100 or fewer nucleotides in length and which is either:

a) at least 80% identical to a contiguous sequence of nucleotides in one of the nucleic acid sequences as shown in Table 3;

b) at least 80% identical to the complement of a contiguous sequence of nucleotides in one of the nucleic acid sequences as shown in Table 3; or

c) capable of selectively hybridizing to said FLAP nucleic acid;

for diagnosing a susceptibility to a disease or condition associated with a FLAP nucleic acid.

34. A method of diagnosing a susceptibility to myocardial infarction in an individual, comprising determining the presence or absence in the individual of a haplotype using one or more of the markers DG00AAFIU, SG13S25, DG00AAJFF, DG00AAHII, DG00AAHID, B_SNP_310657, SG13S30, SG13S32, SG13S42, and SG13S35, with alleles T, G, G, G, T, G, G, A, A and

G at the 13q12 loci comprising a FLAP nucleic acid, wherein the presence of the haplotype is diagnostic of susceptibility to myocardial infarction.

35. The method of Claim 34, wherein determining the presence or absence of the haplotype comprises enzymatic amplification of nucleic acid from the individual.

36. The method of claim 35, wherein determining the presence or absence of the haplotype further comprises electrophoretic analysis.

37. The method of claim 34, wherein determining the presence or absence of the haplotype further comprises restriction fragment length polymorphism analysis.

38. The method of claim 34, wherein determining the presence or absence of the haplotype further comprises sequence analysis.

39. A method of diagnosing a susceptibility to myocardial infarction in an individual, comprising:
obtaining a nucleic acid sample from said individual; and
analyzing the nucleic acid sample for the presence or absence of a haplotype using one or more of the markers DG00AAFIU, SG13S25, DG00AAJFF, DG00AAHII, DG00AAHID, B_SNP_310657, SG13S30, SG13S32, SG13S42, and SG13S35, with alleles T, G, G, G, T, G, G, A, A and G at the 13q12 loci comprising a FLAP nucleic acid, wherein the presence of the haplotype is diagnostic for a susceptibility to myocardial infarction.

40. A method of diagnosing myocardial infarction in an individual, comprising determining the presence or absence in the individual of a haplotype comprising one or more markers and/or single nucleotide polymorphisms as shown in Table 3 in the locus on chromosome 13q12 comprising a FLAP

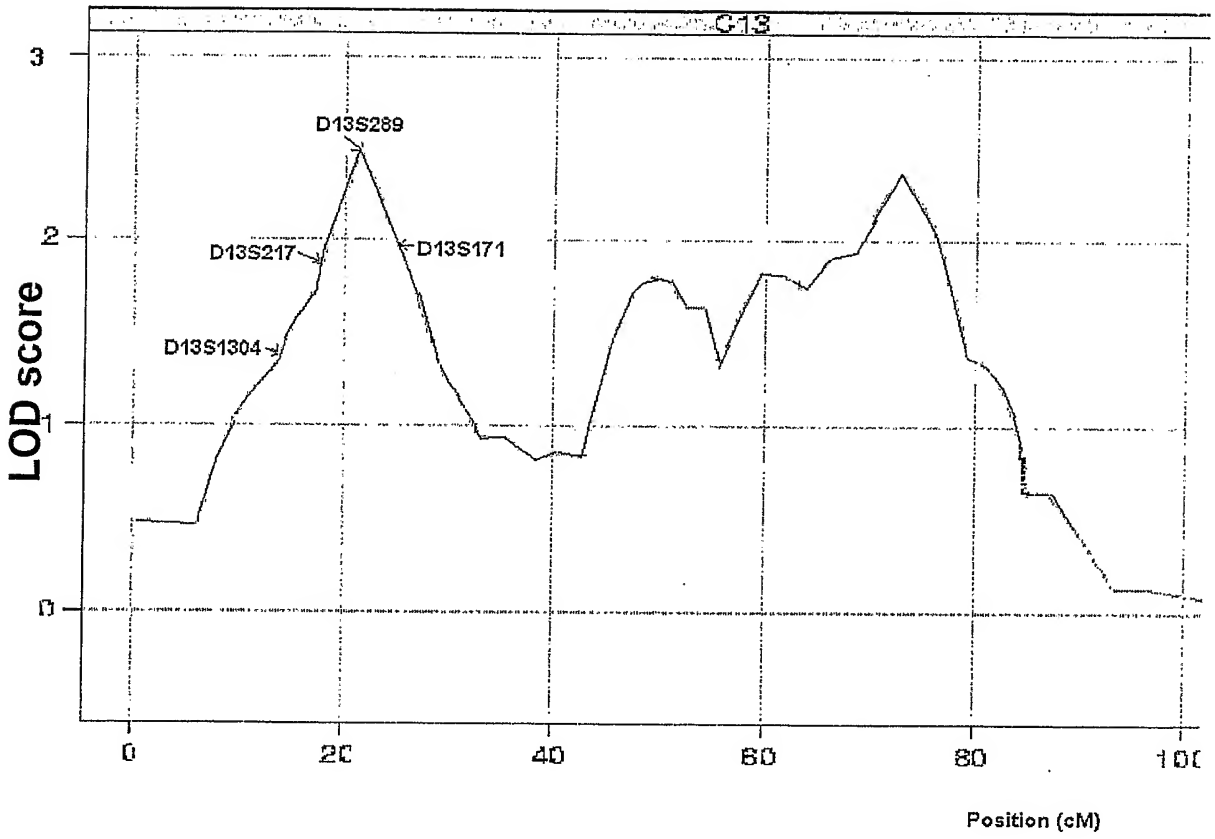
nucleic acid, wherein the presence of the haplotype is diagnostic of myocardial infarction

41. A method of diagnosing a susceptibility to myocardial infarction in an individual, comprising determining the presence or absence in the individual of a haplotype comprising one or more markers and/or single nucleotide polymorphisms as shown in Table 3 in the locus on chromosome 13q12 comprising a FLAP nucleic acid, wherein the presence of the haplotype is diagnostic of a susceptibility to myocardial infarction.

42. A method for the diagnosis and identification of susceptibility to myocardial infarction in an individual, comprising: screening for an at-risk haplotype in the FLAP nucleic acid that is more frequently present in an individual susceptible to myocardial infarction compared to an individual who is not susceptible to myocardial infarction wherein the at-risk haplotype increases the risk significantly.

43. The method of Claim 42 wherein the significant increase is at least about 20%.

44. The method of Claim 42 wherein the significant increase is identified as an odds ratio of at least about 1.2.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0
D13S289
D13S217
D13S171
D13S1304
0
20
40
60
80
100
Position (cM)

FIG. 1

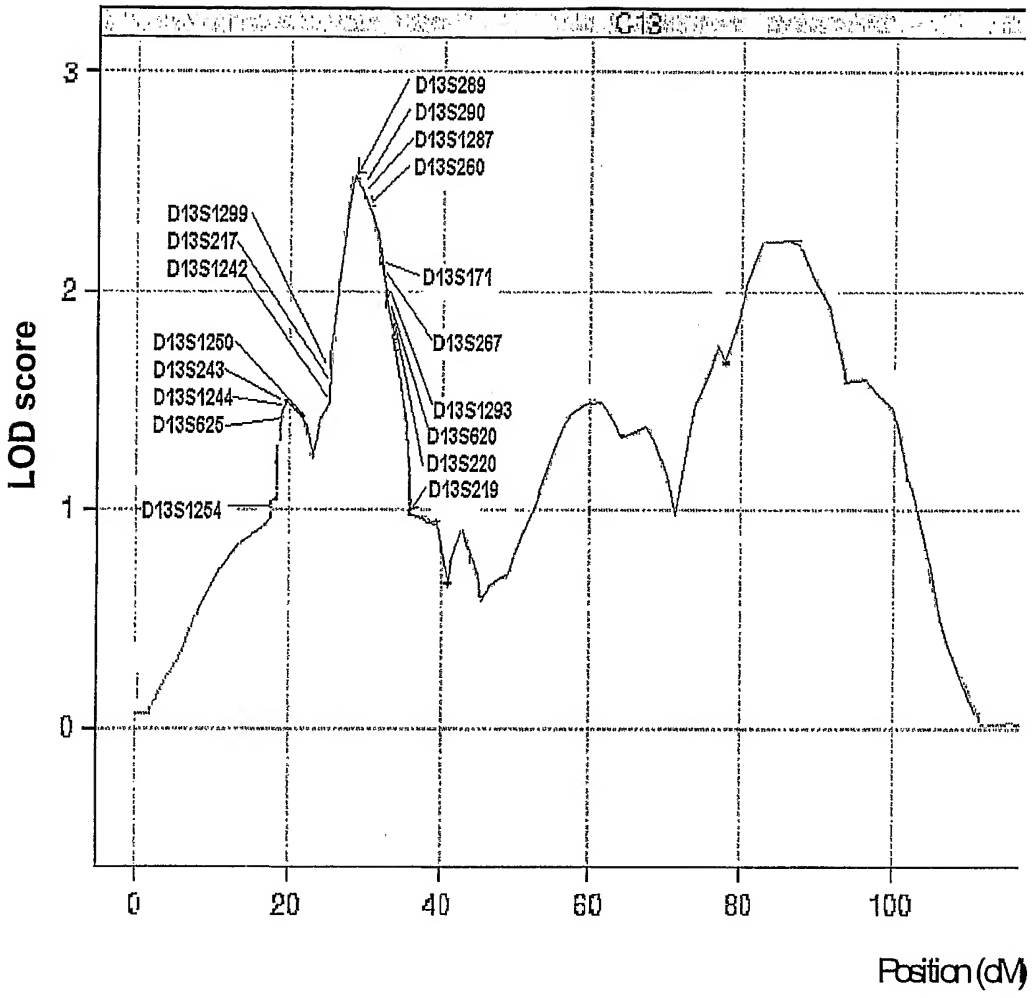

C13
LOD score
3
2
1
0
D13S289
D13S290
D13S1287
D13S260
D13S1299
D13S217
D13S1242
D13S171
D13S1250
D13S243
D13S1244
D13S625
D13S267
D13S1293
D13S620
D13S220
D13S219
D13S1254
0
20
40
60
80
100
Position (cM)

FIG.2

Location of haplotypes showing association (p value< 10^{-5}) with the disease

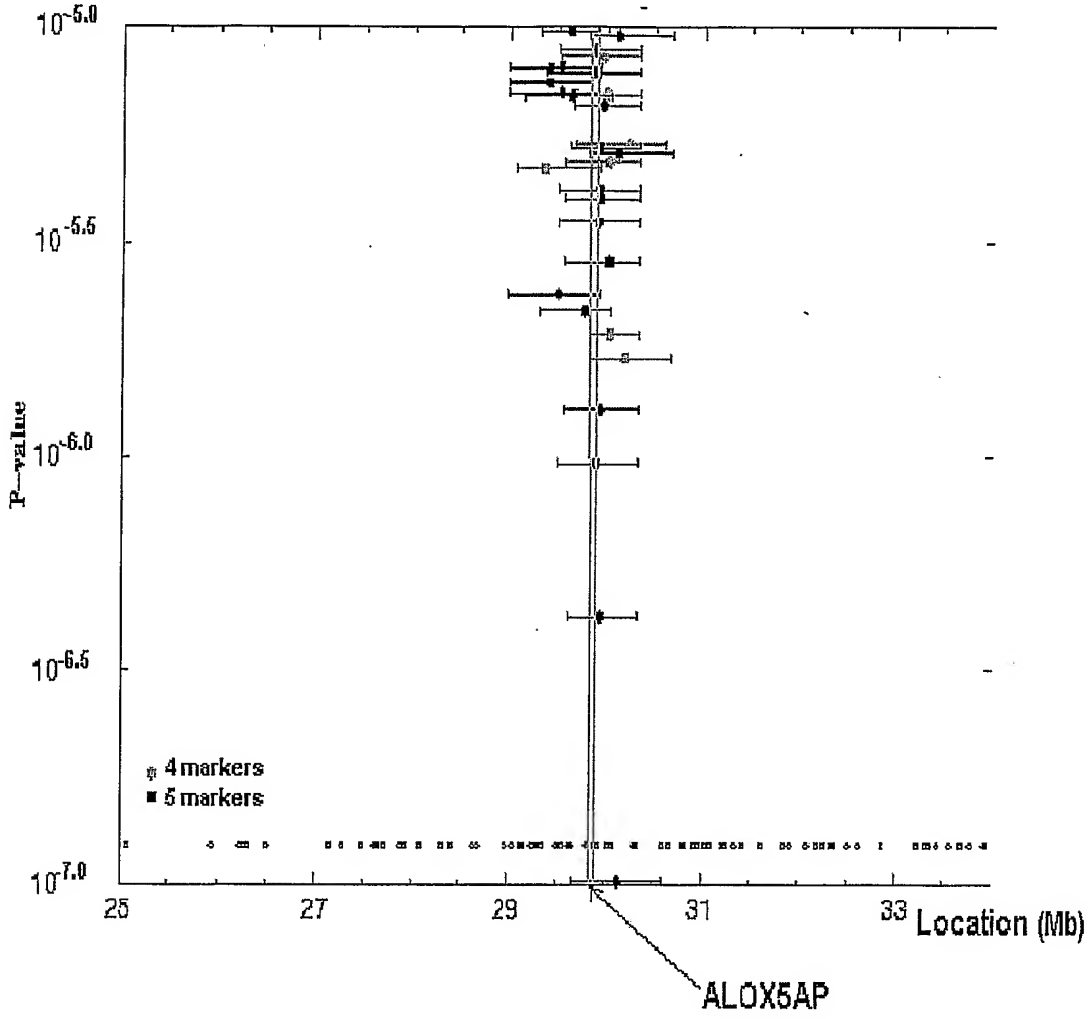


FIG. 3A

Haplotypes showing association (p value< 10^{-5}) with the disease

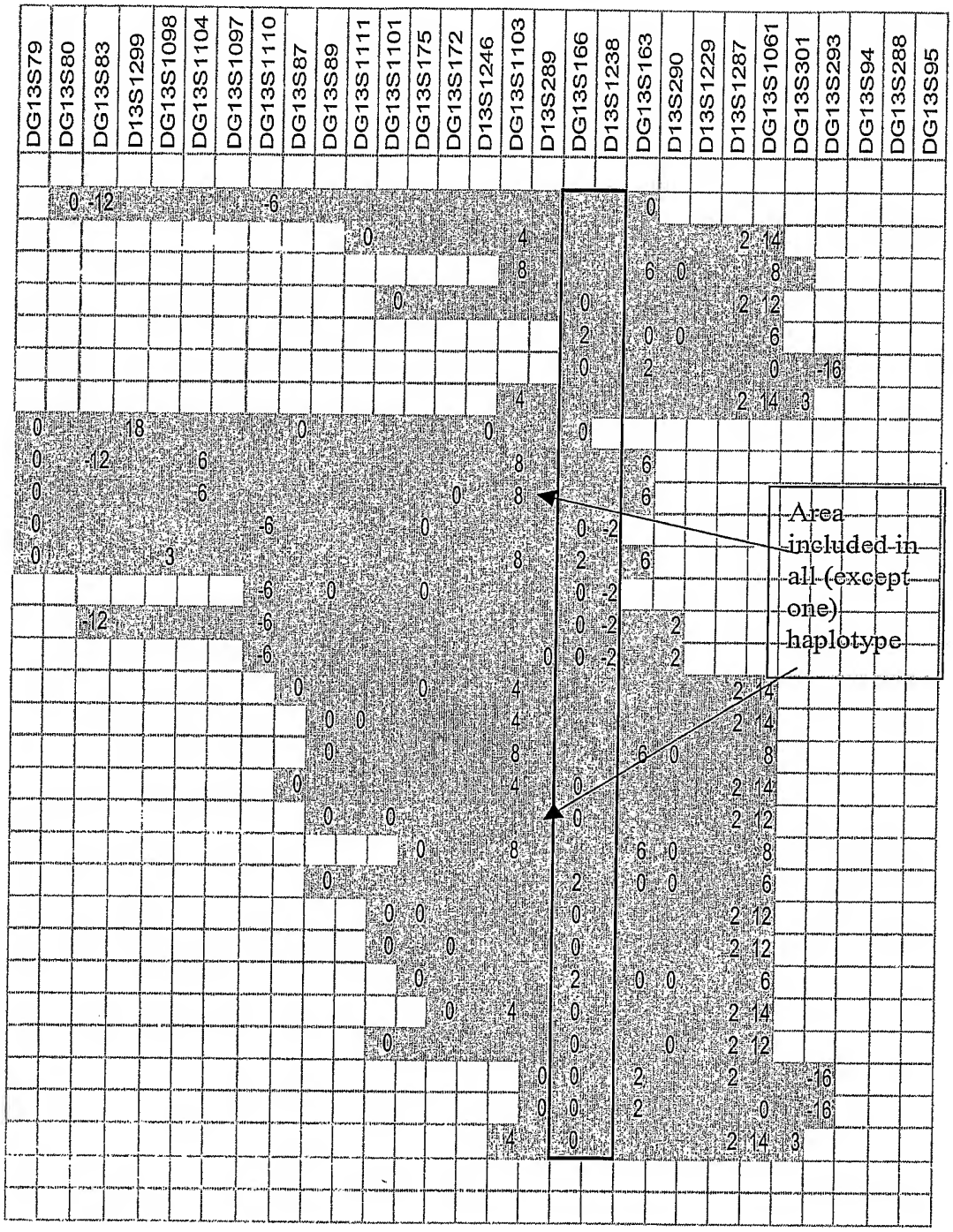


FIG. 3B

Markers and genes around the FLAP gene

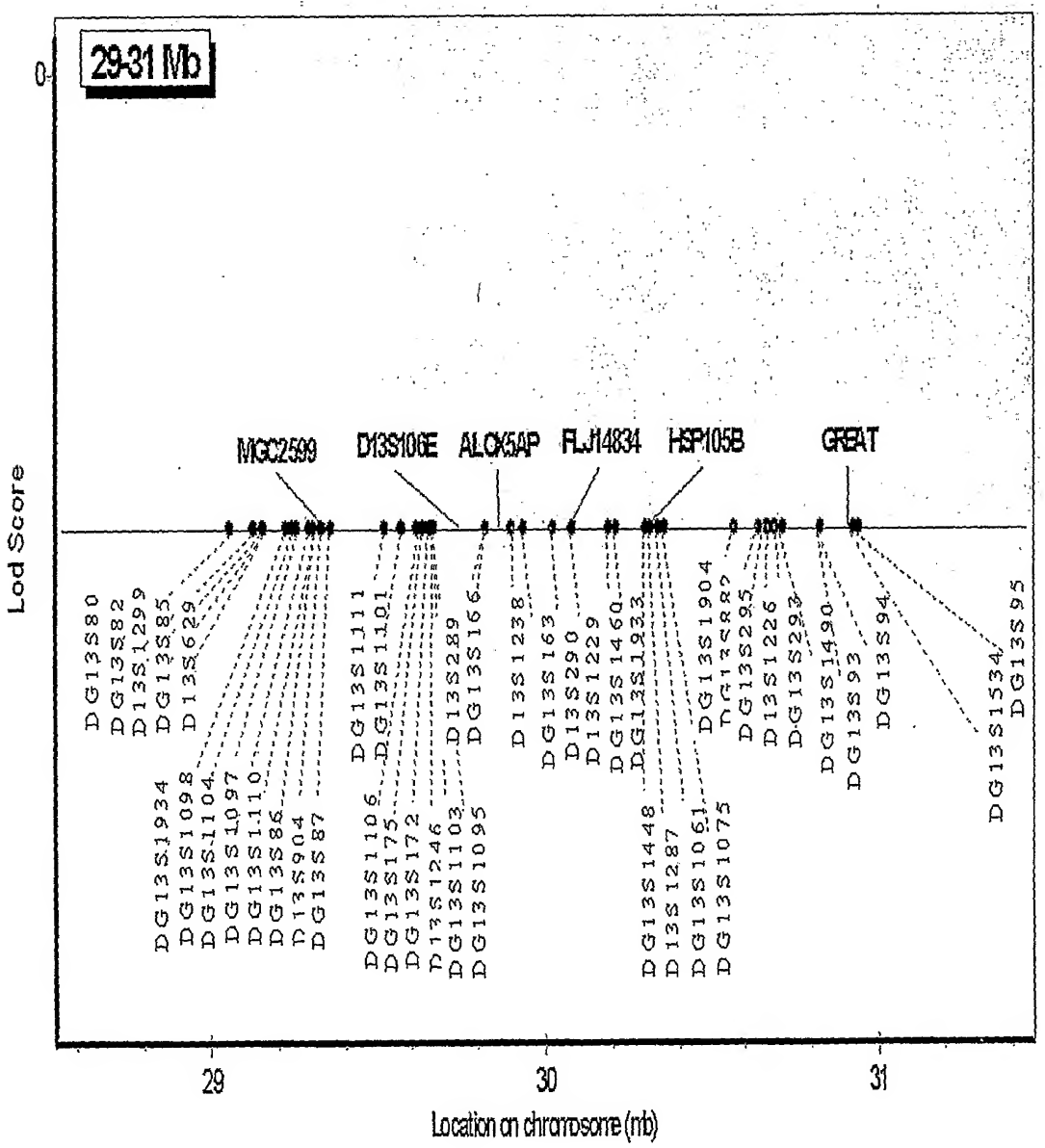
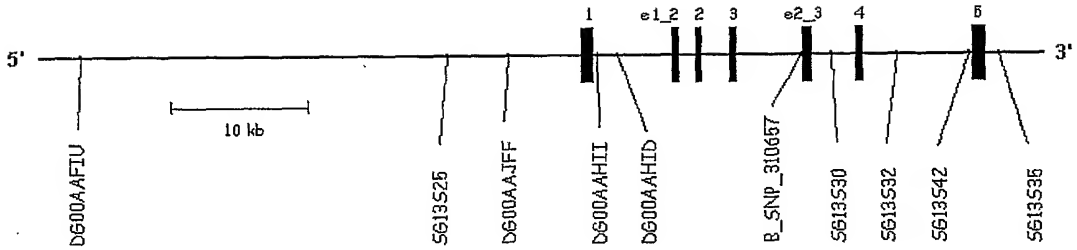


FIG. 4


5'
3'
1
e1_2
2
3
e2_3
4
5
10 kb
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5613525
D600AAJFF
D600AAHII
D600AAHID
B_SNP_310667
5613530
5613532
5613542
5613536

FIG. 5

tacagaccac atgaaaagtg actaaagagc caaaagctgg ggtggccaga gagaaaatgg 60
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FIG. 6A

```
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```

FIG. 6B

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FIG. 6C

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FIG. 6D

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FIG. 6E

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FIG. 6F

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FIG. 6G

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FIG. 6H

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FIG. 6I

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FIG. 6J

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FIG. 6K

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FIG. 6L

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FIG. 6M

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FIG. 6N

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FIG. 60

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FIG. 6P

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FIG. 6Q

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FIG. 6R

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FIG. 6S

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FIG. 6T

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FIG. 6U

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FIG. 6V

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FIG. 6W

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FIG. 6X

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FIG. 6Y

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FIG. 6Z

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FIG. 6A2

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FIG. 6B2

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FIG. 6C2

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FIG. 6D2

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FIG. 6E2

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FIG. 6F2

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FIG. 6G2

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FIG. 6H2

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FIG. 6I2

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FIG. 6J2

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FIG. 6K2

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FIG. 6L2

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FIG. 6M2

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FIG. 6N2

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FIG. 602

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FIG. 6P2

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FIG. 6Q2

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FIG. 6R2

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FIG. 6S2

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FIG. 6T2

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FIG. 6U2

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FIG. 6V2

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FIG. 6W2

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FIG. 6X2

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FIG. 6Y2

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FIG. 6Z2

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FIG. 6A3

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FIG. 6B3

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FIG. 6C3

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FIG. 6D3

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FIG. 6E3

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FIG. 6F3

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FIG. 6G3

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FIG. 6H3

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FIG. 6I3

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FIG. 6J3

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FIG. 6K3

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FIG. 6L3

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FIG. 6M3

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FIG. 6N3

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FIG. 603

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FIG. 6P3

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FIG. 6Q3

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FIG. 6R3

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FIG. 6S3

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FIG. 6T3

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FIG. 6U3

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FIG. 6V3

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FIG. 6W3

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FIG. 6X3

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FIG. 6Y3

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FIG. 6Z3

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FIG. 6A4

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FIG. 6B4

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FIG. 6C4

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FIG. 6D4

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FIG. 6E4

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FIG. 6F4

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FIG. 6G4

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FIG. 6H4

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FIG. 6I4

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FIG. 6J4

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FIG. 6K4

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FIG. 6L4

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FIG. 6M4

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FIG. 6N4

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FIG. 604

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FIG. 6P4

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FIG. 6Q4

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FIG. 6R4

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FIG. 6S4

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FIG. 6T4

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FIG. 6U4

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ctatgcagag ataacttgct tcctaataaa gtaacttcat ggaaaggtac taggaattga 389160
tttgagtttt ttatagcggg aagttacatc agagaatttt gttttagtcc ctcccgcaat 389220
cagttatggc cccaacagca aacaaatggc acgctcagat tagggtactt tgtggaggtc 389280
ttatttacaa aggtgtgggc aggatgcagg aaggccacaa tgggtagtgc agtgctctgg 389340
gtcagtgaca gctaagttct caccatccct aggtcctgga tggggcagga ggacagagtc 389400
acacagagga gaccatcttg agaagagcag tgacctctca ggtgactcag gagtgactca 389460
ggacaaagtc tgaagcagcc gctccaggag tgaccctgag gagaaggagt ctacccctcac 389520
tccatttcct tccctcattg gccacaccca accagagacc agaggggaag ggagtccctg 389580
atgtggtcca gacaggtgag cttcccaggg gagagagcag gtgctgagtg gactggggtg 389640
gggaaagaga gcacatgctc taatcctaga attgaggtgc agtccaaggt cacacaaatg 389700
gttgaataaa ggagatgggc aacaattcat ccttcattca tctacttagc aaatatattt 389760
tccagtcagc acagtgctag gtcctggaaa tacaaagatg agcaagtagt aactttgttc 389820
cctgctgggc atcctgaggc cttaaggaca ttgagtgaca tcaggtttgg aagctgtggc 389880
agttctattt ttcttaatat catggtctcc tattgctgac agagaattga gatataagct 389940

FIG. 6V4

acagttacta ttttgagtaa gaatctgcct gtatcaatga ctgagagagg ctgggagggg 390000
tctcctcacc cattgaagcc tgaatcccat catttgggtt cagaattggg tcataaagga 390060
ttttttcatt tttgagagtt ccctatgata atgcaacctc cagctctcac cccaggatgg 390120
ttaagtcctt ctgtccccgg ctctcaatac tggctgctct tgggaatcac cgggagagcc 390180
ttcaagaatg cagatacagg ctgggcgggg tggcttacac ctgtaattcc agcactttgg 390240
gaggctgagg caggaggatc ccttgagacg aggagttcaa gaccagcctg ggcaacgtag 390300
taaaattctg tttctacaaa aaataaataa attagctggg cgtggtggtg catgcctgta 390360
gtccttggga ggctacttgg gaggctgagg tgggaggatc ccttgagccc aggagttcaa 390420
ggctgcggta gtgagctgtg attgcaccac tgcacttcaa catgggtgac agagcaagat 390480
cctgtctcta aacaaacaaa acaaaaccaa aagcaaaaca cagatacctg ggcctactcc 390540
cagaaattct gtttaactgg ccagtgggac ccagcctgct acatgtttag attctcacct 390600
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caaagacctt tacagttttg ttcagtgtgg gccacgctgg ggtgggggac atacgtgaac 390780
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gatattttgc attaattttg atttgcatta aaatatcagt tatggtgatc actgagttct 391080
ctggtgctcc tttccttttt ttgttttgtt ttttgccag agctggtgag actcagctca 391140
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cagcttatga ttatgggaat aggttttgtt tgcaatggga caaacttgga tttgaacctc 391260
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tgtaatctcc tggggataac agaaatccct aggctaggtg gtagggctgc cagggtgaaa 391380
gtcacacatc agacgtacct gcagtgccat ggcaggacct gcatagagcg ggccaccaga 391440
atgggtttcg tcaagggtcc tgggtggcag tgcatggcac taaggctgag tgaggcatgc 391500
ttgttaccct gcactccccc cagnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 391560
nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 391620
nnnccgcgga gtcctgtcc ccgcagcaca cagaggcccc tttgtctctg gcccacacct 391680
gactgcggct cagcaaggcg gtgacagcac tgctggcgcg cagccaggca ataacaacat 391740
tagtcatgcc ttttccagaa aggcctcgta aacctgcaag ggtctgggtg cccctaggtg 391800
gccctgggcg ggtgtttttc atttcctttg cctgttgatt tttaaatgca gctgcttttt 391860
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ggggaccatc accaccttgg cccctgcaga cctgaacact gagcattgtg agttctgggg 391980
tcaacggctc cagacacaaa ggcgaatctg tgggtttccc ctgggccatt ggagaaaacc 392040
ctgtggcagc tccttttttc cttccttccc agagcaccct gttgcccatc acctggcact 392100
ggcaacccct gaggtgcagg ccactcctta ctaggggttt tctttttttc ttcttctttt 392160
tttgttttga gacgaagttt tgctcttgtt gcccaggctg gagtgcagtg gcaccatctc 392220
tgctcactgc aacatttgct tcctgggttc aagcgattct cctgcttcag cctcctgagc 392280
agctgggatt agaggcgtgt accaccatgc cgggctaatt ttgtattttt agtagagatg 392340
gagtttcacc atgttggcca ggctggtctc gaactcctga cctcaagtga tctacccgcc 392400
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cctttgccat ggtaactggc aatgtcctag atagtggcct ccccgtcctg tccccccacc 393000
ctcatcaacc tggggcctgg agtgaggact atgagccgct gaccgtggtt gcccccttagc 393060
ataacctggc ccatcccgcc tgctgcactg accggccctc ccagcttggc acaggccata 393120
gagacaggca ggaaaaatac aatttcttga cccccttataa acctgcagag ttttcttggt 393180
gagctgggag actctgcagc aggtcagaga agcaccctaa gtgcgtggca cccatgactc 393240
tccatctgct catgccttgc ctatctttaa aaggtggatg aaatattatt tacagcatga 393300
agccttctat aaatagggtg gacggcctta ccacataaaa acccaggaca cacagctgaa 393360
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tgtgacatac ttatactaaa acttatgcat tgtttatctg aaattcaaat tcagctgggt 393480
gtcttgtatt ttatcaggaa atcctatcta taatctttct ttcctctaac caatatagca 393540
tttataactc tatttatgac tttctgccca ggattgtaat aatgatgttc ccatttttatc 393600
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gcccccaacc cagacccctc gcttagtaca ggcattaact taacgaaaaa gttggttctg 393720
atgtggcgga aggcttttag aggtgctcaa agagaaaaaa aaggacagca caaagaatta 393780
gacatttgtg tttttctcgc ttccttccaa ataacatcag agtctagcat tttgtatttt 393840

FIG. 6W4

gcggtgacca tggacctagc agctggaagg agaccctaac ttcttttcta ggttgttatc 393900
gtcctttccc agcagaccct atgctggaaa ctgagctagt acttccaggg tccgtgcgcc 393960
tctctgagaa gctgctctgc aaactcttgc atcctcgtgg gtatgggggc actgggaggc 394020
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gcacacaggt agatgaactt ccgcggctcc tccaaggcat caactctgct aaagaaccct 394140
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cacacgccat gctttcgacc ttagaaatca gcgttgggag catcaaggtt cctgcatgtt 394260
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tgctggatca taaggagccc taagccaagg atggcggctg cttttggtgt ctatggtctc 395280
cccagcccta acacagtgcc gggcgtgcaa cacatgcctg ctgaatgaat gggtgagtga 395340
atgctgaaga aataaatgat gtgcacttta ctttatgctc ggtttttttct ttgggctcac 395400
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aaggcatcaa ggacagccat gacccagttt agcaatccag atctcaccct gactcccgtt 395520
gcatttcttt tgagttctta tttttctttc tgcatctgta gatgttcctt tttctctgtc 395580
cagggtcaac ccaagcatgg gatagacccc cttggcttcc tgcaacacct tccacgccca 395640
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accacatcct gagctttccc tgctcctctg tcttctttcc caatttctct caccccccgaa 395760
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ggaggcttat cttctatttc aaagcagttt atctacgtat tttgctaaac atgggcagtc 396060
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ccacatattt ttgagaactg ctagggtcca atatggccag aacgtagggt gtgaggcgca 396180
gggccagatg aagatggcaa ggttaagtgg gcctgctctg gaggaccctg caggccaggc 396240
caaggtacat gcatcttatc ttagaggcag aaggagccat ggatgtaagc agggatcaga 396300
ggttcccaga aggtgagttt agagcctggg aaacgaggta ggagggaatg taatgagttc 396360
agtcagaaga gtgggcatga gcaggggcgg tgtggtggag aggaaaggga caggaggcgt 396420
gccttgggat agacaggact ccctggctgc ttagatatga catggaaggg agaggacaga 396480
ctgagatact gtcacatttc tagcttgagc aatgtgtgac tgtcatgctg ctcttggaga 396540
tggagcagta ggagggaaac aggccccggt cagtgttcac atgcgggatg cagagcaaac 396600
ggagcccaag gccaatgaca gacannnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 396660
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nnnnttctta cattgcatga gtgcaaaggg gacattgaaa tatgtatttt cagtaaatga 396780
tacccataag cctctgtgtc ttgtgtaaca ttcacagttc atgtgttaat tctggcccaa 396840
gcctgctcat aaacaggtta ttccacaagt cccaatcacg aatgatggaa ggaagctatt 396900
ttaaagatca gactgtaaac tttttaggtt aaaggtccac taaagactca gcggctttgt 396960
gtttgtcaag taaaatcaag tatcacttac acacaaccag ataaaccagt ctggaagttg 397020
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tttattaaaa agctacacta gatcgtgacc aagctattga cctcttaatg taacggtgtt 397200
aatttattga gttgatttga ttttagtaag tgtgtgtgtg tatatcctat ttgtaatcac 397260
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ttcaaaaaac agaattgaaa tattttaaat taaaaatgga tacaaacatg tgaattctta 397380
aactattttg ttttatctat attatttcct agagtacaaa agaaagatat tttatgattt 397440
tatgatcatt tatgagcaag agtaaaaaat tactatggaa aatagaatta tgtacaacta 397500
aaacattttc aaatgtcaaa agtattctat attgttcatt tttaaagtaa ccaatttgta 397560
ataaataaaa taagtgttat tttggtattt atatgtatta atattgtttt attaatagac 397620
acgaacgcac gcacacacgc acacacacac acacttaaag taaaaactgt tagccctcct 397680
attaaatttt aattacttaa aaatatctcc taggtgctcc ttaactaaaa aattcaacta 397740

FIG. 6X4

atttctaaac aataatttga ataactagtt cataataact catttaaatt gtctttgccc 397800
tgacgacagc acatggtatt ttactaatta attaaaaaat aattattgag cttaaagtgc 397860
aaattaaagg ctcaactaga taaattaggt taattagata agtctatagg taactgaaaa 397920
taaaaatgat catttctgaa aattattctg ggctaataat tttgacctta aaattagttt 397980
taacgctttt taaaactgca gtcaaactaa aagaaataac attttctcaa taagaaaaaa 398040
attatattat aggaaatgtt ttattatttt aaaagaatat tataggaaat ggaaaaatcc 398100
tttgctctgt gaaacatcat ttgataaata ttggcaaaag aatcacaatg ttcacaggag 398160
ggctcctcat tcggccctca tctgtatact tctacattga ttggcttcat ataatccctt 398220
atgacgcagt aaaacccagc agtcagcttc atcaagtgag cgccaaataa aacaaaattg 398280
actaaaggtt aattctacta ctttgaaaag agttttgaac tcagtgttga aggtaacgag 398340
ttaattaaat tgctcattac ttcaacttaa atggagtaag ttcacagtac tcatatagat 398400
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aatggactta agttaagtta acttttttatg gagcagttat taatttcagt acttgaatta 398700
gtaacatttg ttatttgttt taaattgagt tcatactttt caaaattcta aatgtttctc 398760
acttgcacag cagctctttt gatcatttca tctttcttgg 398800

FIG. 6Y4

Amino acid sequence of FLAP (>alox5ap_protein translation NM_01629)
MDQETVGNVVLLAIVTLISVVQNGFFAHKVEHESRTQN
GRSFQRTGTLAFERVYTANQNCVDAYPTFLAVLWSAGL
LCSQVPAAFAGLMYLFVRQKYFVGYLGERTQSTPGYIFGK
RIILFLFLMSVAGIFNYYLIFFFGSDFENYIKTISTTISPLLLIP
(SEQ ID NO: 2)

MRNA of FLAP (NM_001629_mRNA)
Acttccccttcctgtacagggcaggttgtgcagctggaggcagagcagtcctctctggggagcctgaagcaaacatgga
tcaagaaactgtaggcaatgttgtcctgttggccatcgtcaccctcatcagcgtggtccagaatggattctttgcccataaag
tggagcacgaaagcaggacccagaatgggaggagcttccagaggaccggaacacttgcctttgagcgggtctacactg
ccaaccagaactgtgtagatgcgtaccccactttcctcgctgtgctctggtctgcggggctactttgcagccaagttcctgct
gcgtttgctggactgatgtacttgtttgtgaggcaaaagtactttgtcggttacctaggagagagaacgcagagcacccctg
gctacatatttgggaaacgcatcatactcttcctgttcctcatgtccgttgctggcatattcaactattacctcatcttcttttcgg
aagtgactttgaaaactacataaagacgatctccaccaccatctcccctctacttctcattccctaactctctgctgaatatgg
ggttggtgttctcatctaatcaatacctacaagtcatcataattcagctcttgagagcattctgctcttctttagatggctgtaaat
ctattggccatctgggcttcacagcttgagttaaccttgcttttccgggaacaaaatgatgtcatgtcagctccgccccttgaa
catgaccgtggccccaaatttgctattcccatgcattttgtttgtttcttcacttatcctgttctctgaagatgttttgtgaccaggt
ttgtgttttcttaaaataaaatgcagagacatgtttt (SEQ ID NO: 3)

FIG. 7A

FLA310657 / B_SNP_310657 (R = G/A) (SEQ ID NO: 398)
GGGCTACTTTGCAGCCAAGGTAACTCAGACTTCCCTTTGTTCATTCTCCTTCTATAAAGTGCATCTCAA
GGAGGTTCAAAGGGCAGGCTTTTTGTTGAAAGGACTTTGCCTGACCTCTGGCTCCCATCTGTGAAGCCC
TGGAGAGGTGAGAGCCCTCGGGAGGCCGTGTTTCAGGCATGCTCTGCACCCGTGCAGAGCGC
R
TGTGATAATGCATTGCTAATGCTTGCTCCCTGGTGGCTGGCTGAGAGCTGCTGTGCTGACAAGGGTGGT
TTAAGGCTAAATGTGACTCAGAATCCTTAAGCAGTGTTAGTTCAGATACAAGGGCATTATAAATGAGAG
TGCCTGAGGGATCTATTTTGGGACCGCTGTCACTTGGCTCTTCTGCTAATAAGCTTCCAGTG

FLA302465 (Y = C/T) (SEQ ID NO: 399)
GTTTCTGCTAAATGACAGTTGATGGAGGACATTTAGGGTTGCTTGGAGGTCAAGTCAAGGAGGCATTTA
ACATTCTAGTAAAACAAGGAAGTAACAGGCTCCTGAACATGCCCACAATGAACCAGATGCAAACCTTTT
CCCTTGGCAGGATTCTTTGCCCATAAAGTGGAGCACGAAAGCAGGACCCAGAATGGGAGGAG
Y
TTCCAGAGGACCGGAACACTTGCCTTTGAGCGGGTCTACACTGCCAAGTGAGTCCTAACCCTGATGTTG
CTAATAAGTGGGGGCATGGGCAGGGGGGCCTCCTTCTAGGAGTGATGACCACCCTTAATACCACATGTC
TGTCTGAGCCAAGTTTCTGAGCGCCAGGGAGGTGAGGAAGGTTGGACTTCACCAGAGAGGCT

FLA302524 / B_SNP_302524 (M = C/A) (SEQ ID NO: 400)
GAGGCATTTAACATTCTAGTAAAACAAGGAAGTAACAGGCTCCTGAACATGCCCACAATGAACCAGATG
CAAACCTTTTCCCTTGGCAGGATTCTTTGCCCATAAAGTGGAGCACGAAAGCAGGACCCAGAATGGGAG
GAGCTTCCAGAGGACCGGAACACTTGCCTTTGAGCGGGTCTACACTGCCAAGTGAGTCCTAA
M
CCTGATGTTGCTAATAAGTGGGGGCATGGGCAGGGGGGCCTCCTTCTAGGAGTGATGACCACCCTTAAT
ACCACATGTCTGTCTGAGCCAAGTTTCTGAGCGCCAGGGAGGTGAGGAAGGTTGGACTTCACCAGAGAG
GCTTTGTGGACACCCTTTATCATCTTAGTGAGTGCTAGTGTCAAAACAAAGGGAGTGGGGAT

B_SNP_302560 (R=G/A) (SEQ ID NO: 401)
CAGGCTCCTGAACATGCCCACAATGAACCAGATGCAAACCTTTTCCCTTGGCAGGATTCTTTGCCCATA
AAGTGGAGCACGAAAGCAGGACCCAGAATGGGAGGAGCTTCCAGAGGACCGGAACACTTGCCTTTGAGC
GGGTCTACACTGCCAAGTGAGTCCTAACCCTGATGTTGCTAATAAGTGGGGGCATGGGCAGG
R
GGGCCTCCTTCTAGGAGTGATGACCACCCTTAATACCACATGTCTGTCTGAGCCAAGTTTCTGAGCGCC
AGGGAGGTGAGGAAGGTTGGACTTCACCAGAGAGGCTTTGTGGACACCCTTTATCATCTTAGTGAGTGC
TAGTGTCAAAACAAAGGGAGTGGGGATATGGGGCACATTGGTGGAGGGAGGTGTGATCTCTG

B_SNP_302617 (Y=C/T) (SEQ ID NO: 402)
CTTTGCCCATAAAGTGGAGCACGAAAGCAGGACCCAGAATGGGAGGAGCTTCCAGAGGACCGGAACACT
TGCCTTTGAGCGGGTCTACACTGCCAAGTGAGTCCTAACCCTGATGTTGCTAATAAGTGGGGGCATGGG
CAGGGGGGCCTCCTTCTAGGAGTGATGACCACCCTTAATACCACATGTCTGTCTGAGCCAAG
Y
TTCTGAGCGCCAGGGAGGTGAGGAAGGTTGGACTTCACCAGAGAGGCTTTGTGGACACCCTTTATCATC
TTAGTGAGTGCTAGTGTCAAAACAAAGGGAGTGGGGATATGGGGCACATTGGTGGAGGGAGGTGTGATC
TCTGCAGCTTCAGAAAGATCTGAAAGAGTCATTTGGTTAGAGAAGTTGACCTATTTCCTGTG

FLA314500 (S = G/C) (SEQ ID NO: 403)
CTGCTGCGTTTGCTGGACTGATGTACTTGTTTGTGAGGCAAAAGTACTTTGTCGGTTACCTAGGAGAGA
GAACGCAGAGGTAGGTAACTGGGACTACTAAAGAACTGTGGAGCGATTCCTGATTTTTGAGCAGGAAGA
GTGACAATTCAAAACAGTATTTGACTAGATTCACGGCTCCGTAGCATCCCCTTGGGTGGGAG
S
GGGAAGGCTGACTAGGACCTCTGATTCTTCTTTCCCTGAGCTTTGAAGGCTCTGAAAATACAGCTGGGG
GGACTTGCCCAGTTTTCTTATTAAGCAATTCCTCCGCATGGTGCTGGCTTTCAAAGGGTGCTTCAGTGC
TGTTTGCTGCACGTGCCTTGCAGCCCCACACCCTGCACTCCCGCCCTGCAGAGTCTGGCGCT

FLA267479 (R = G/A) (SEQ ID NO: 404)
CTCATGGATTTTGTTTTCCAAGTGGCAAGATGGCGCCTCCACCTTTGGTATCCTATTTTAGTTCCTGGC
AGAAAGAAAGGAACAGGCTAATGGCCCTGATGAGTCTACCCCCTTTTAACAGGAGAAAATTTAAAAAAC
AAAAACCATGAAACCCTTTCCCAGAGGCAACAACCAGAATTCCATTTATCTTTCATTGACCA
R

FIG. 7B

AACAGACCACATGGTCACTGGTGGTGGCAATGGAGACTGGGGAGATGAATATTTTTAAGGTGGCATATT
CCAGAAGAACACTGTGCACTGATTGCATTAATGAACCCATTAATGTGCCAAGGGGAGGTTTACCTATGA
GCATGGGCAAATTAGAACCCACTCTTGGAGCTGCAGGTGAGCCAATCCCACCTAAACAGTGT

FLA267696 (R = G/A) (SEQ ID NO: 405)
ACTGGTGGTGGCAATGGAGACTGGGGAGATGAATATTTTTAAGGTGGCATATTCCAGAAGAACACTGTG
CACTGATTGCATTAATGAACCCATTAATGTGCCAAGGGGAGGTTTACCTATGAGCATGGGCAAATTAGA
ACCCACTCTTGGAGCTGCAGGTGAGCCAATCCCACCTAAACAGTGTGGATGCTACAAGATGG
R
GAAGTAAATTGATTCTATTCCATACCCTAACCTCTCTCCAAGATGTATTCTTAAAATAGAAGAGGGAAG
ACAGAAGAAAACATCCAGAATATATTTTTATTGTCTTTTACTTCTTCAGTGCATTTTAGATCAGTGCTT
CTCAATCTGGCAAGGGGCATGCAGGAGGATGTGAGTTTTATCAGGAAAACTACACAACCCCC

FLA267853 (R = G/A) (SEQ ID NO: 406)
GGTGAGCCAATCCCACCTAAACAGTGTGGATGCTACAAGATGGGGAAGTAAATTGATTCTATTCCATAC
CCTAACCTCTCTCCAAGATGTATTCTTAAAATAGAAGAGGGAAGACAGAAGAAAACATCCAGAATATAT
TTTTATTGTCTTTTACTTCTTCAGTGCATTTTAGATCAGTGCTTCTCAATCTGGCAAGGGGC
R
TGCAGGAGGATGTGAGTTTTATCAGGAAAACTACACAACCCCCCAACCACAATGCTACCCCCACTCCTG
TGGACCTTCTTTAAGAGAGACTCACTATTATAGATGGAGTTGATACGATTTTAAGAGAGGCCATATATT
ATTTGCTTTCTGTCTTGAAAAACTTGTGATTTTTCTGTATTGTGCTACTGCCAAAGAGAATA

FLA270742 (Y = C/T) (SEQ ID NO: 407)
TGTTGCAGTTCTCATTGCTGGGGAGTCTAAACTGGAATAAAACACCCACTATCTCCATCAGGCTTGCAC
TAGAGCCCAGCTCTAGCTGGAGAGAAAGAAGCTAACCCGCACAGACACAGGACTGTAGGCAGGGAGCAT
CCGGGGGTATTTGGGTCCTGGCTCTGATGTGCCTAAGGCCAACTTCTCTCTGGCCATGCTGG
Y
GTGCATGAGCTCACTAATCTTCCTTTTTGCCTTCCATTTTCTCCAATCCTGACTTAGCAAAGGTTGGGC
AAAAGAGACTCTGTGTGAGTTCGAGCAAAGCCTGAGATGCTGGATTTTCCAAGATACGAGAAGGGGCTG
GGGGCTGGGTGAACTGGTGGTGGAGGAGGGAAGGATTAATTTCCCAAGGAGGGGAAGGGGCC

FLA270830 (R = G/A) (SEQ ID NO: 408)
GAGAGAAAGAAGCTAACCCGCACAGACACAGGACTGTAGGCAGGGAGCATCCGGGGGTATTTGGGTCCT
GGCTCTGATGTGCCTAAGGCCAACTTCTCTCTGGCCATGCTGGCGTGCATGAGCTCACTAATCTTCCTT
TTTGCCTTCCATTTTCTCCAATCCTGACTTAGCAAAGGTTGGGCAAAAGAGACTCTGTGTGA
R
TTCGAGCAAAGCCTGAGATGCTGGATTTTCCAAGATACGAGAAGGGGCTGGGGGCTGGGTGAACTGGTG
GTGGAGGAGGGAAGGATTAATTTCCCAAGGAGGGGAAGGGGCCAGGACATCAGGCCCCGGGGACTTTGA
AGAGAGGGTCGTGGGTAGGAGGTAGATCAAGTGGAGTGACACAAAGGTCAGGAAAGAGGAAG

FLA273407 (W = T/A) (SEQ ID NO: 409)
GCTTTAACTTGTCACATGACTATGGCCAAGTTCCTGGGGCTCTCCAAGCTTCACTTCCTCTGTAAAAAG
GGCAATAATATAATACCTGTCTTATTGGGTTTTGTCCATGTTAGATGAGACATTGGGTACAAAGCACTT
GGTCCCGTGCCTGGCACATTTACTGCACTTAATGTATGATAGTTTTCTTATTATTCTAATAA
W
CAATATGGCTTTGGGAGTATAGTTCTGCCACATTGCAGTGGCCAGAGTGAAGGTGGTGAGTGCCTTCTG
GGGCCCTGGGAGTCAAGGTTATCCGCATGCCCTTTCTTGCTTGCTCCTCAGTGTGGCTGCCTCTATGTC
CACACCATGCAGATGCAACAGGTAGTTTGAACCTCTGAGGCCCACAGTGGGATGGGGAGGCA

FLA274084 (R = G/A) (SEQ ID NO: 410)
TACCGAATCCAGCATTCAAAGTGATGGAAATATGTATATATAGTAATAGTAAAATATCAGCACTTAATG
GCCTGATAAGAATGTCACTGCAATGCTGAGTTTGGACCAACATTTGCCTGCTCCTGCCATTGAGCCCGG
GCTCCCCTCCAGAGCTGAGCTGCTGCAAGGGATCTGAGTAACTAGGGCTGTGTCAGAGTGGC
R
ATGACAGCCACCACATGCTAAGGAAGAGATCCCCAAGGACAAGGAGAATCCCACGTGGAGCTACTTGCT
TCTTTGTCAGTCTTGTTTTTCTTATTTCACAACCTTCTAAAACACAATCTCTCAACCTCTATTGTTAGC
TTGCATTTTTCAATCATGAGCACAGCTTTACCTGGCTCCATGCTTTGATTGACTCTACCTGC

FLA275784 (Y = C/T) (SEQ ID NO: 411)

FIG. 7C

GAGTGGCTCACAGAACTCAGGGAAACACAGCTACCAGTTTATTGCGAAGGACATTTTAAAGGATAAAAG
TAGGCAGATAAAGAGATGCATAGGGCGAGGTGTGGAAAGGTCCCTAGTGCAGGAGCTTCTGTCCATGTG
GAGCGGGGGTGCACCACCCTCTCAGTACATGAATGAGTTCTCCTTCACCTGCCTATCAGCCT
Y
TACATGTTCAGCTCCCCAACCCAGTCCTCTTGGGTTTTTATGGAAGCTTCAAGACACCCACATTCTTTC
CCCAGAGTATAGGGCAAGACCTTCTCTGGGGAGGGTTTTAAGACCCACAGTCAGAAAGGTGGGGTGGGG
TCAAGATTAGAGTCCTGCCTTGACGGGCAGGTGAAAGGGGTAGGGGGAGTAGGTGAGAAAAA

FLA275952 (R = G/A) (SEQ ID NO: 412)
GAATGAGTTCTCCTTCACCTGCCTATCAGCCTCTACATGTTCAGCTCCCCAACCCAGTCCTCTTGGGTT
TTTATGGAAGCTTCAAGACACCCACATTCTTTCCCCAGAGTATAGGGCAAGACCTTCTCTGGGGAGGGT
TTTAAGACCCACAGTCAGAAAGGTGGGGTGGGGTCAAGATTAGAGTCCTGCCTTGACGGGCA
R
GTGAAAGGGGTAGGGGGAGTAGGTGAGAAAAATTCTGTTTATTTTTTCTTTTTTTTTTTGAGACGGAGT
TTCACTCTTGTTGCCCAGGGTGGAGTGCAATGGCACAATCTCAGCTCACTGCAACCTCCGCCTCCCAGG
TTTAAGCGATTCTCCTGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCGTGTGCCACCATG

FLA277478 (R = G/A) (SEQ ID NO: 413)
CTGGTATACCTAGAAAACATTCCATAAAAGTTAGTAATTGTTGGTCATGTAATGATGACTCTCTAGGCT
AGGATTTCAGCTTCATTGCATGCACATGGTGCACTCACAGGGCGTGACCTCTCTCTGTCTCAGTAACCT
CATCTGAGGACCGGGATAATCATACCGCTTCAAAGGGATGTCATAAAGATTAAATAATATGT
R
TAAGGCTGCTTGCATTTAGCTGCATTCAACAAATATTTCTGTATCTTTCTCCTCATTTCTCCTTACTTT
CTTGCTTATTATCTGCTCTAGGTATAGATTTCAGAGAACTAAGCTTGTTACAATCCTTCATAAAATAAC
CAGGTTGGTTAGGGCATTTCCAAGAGTCAATACTGTTTAGTGACTATTCTCTGTTTAATCTA

FLA277678 (M = C/A) (SEQ ID NO: 414)
GTAAGGCTGCTTGCATTTAGCTGCATTCAACAAATATTTCTGTATCTTTCTCCTCATTTCTCCTTACTT
TCTTGCTTATTATCTGCTCTAGGTATAGATTTCAGAGAACTAAGCTTGTTACAATCCTTCATAAAATAA
CCAGGTTGGTTAGGGCATTTCCAAGAGTCAATACTGTTTAGTGACTATTCTCTGTTTAATCT
M
TTTTGATTGTCCAGGGTCATCTTTTGCTATGTCATAGGTTGTTGGCTTCTTCTAGAGAAGTGAGACGAT
GGACAAGTTCCAAGTGAGTGAGGCGACTGGTCAGGATATTCCGCTGAAAAACTCATGTCAGTTCTAATT
CGTGATTGTAATTCAATCACAGCCTGAGAACAGTAGGACTGTAGTTCAAATGCTCTGTTCCC

FLA278185 (R = G/A) (SEQ ID NO: 415)
CTCCTGGGTTCAAGCAATTCTCCTGCCTCAGCCTCCCAAGTAGCTGGGACTACAGGCACATGCCACCAC
GCCCAGATAATTTTCGTATTTTTAGTAGAGACGGGGTTTCCCCTTGTTGGCCAGGGTGGTCTTGATCTC
TTGACCTCATGATCCGCCCACCTCGGCCTCCCAAAGTGCTGGGATTACAGGCGTGAGCCACC
R
CGCCCGGCCTCTAGAGGATAATTTTTAAATGTGCTTTTGCATTTGGAAAATGTGATTGGCATTTTTTTC
TAATTTTCTAATATGATACGCTGTCGGATGCTATGGATTACTTAAACCCTCTGGCTACCTAGAAAGATC
TTTAAGTGGTTCTCAACAAGCTTCATACGCAATGTAAATTGTATTATCTCTCAGGATGTGTG

FLA278492 (R = G/A) (SEQ ID NO: 416)
TTACTTAAACCCTCTGGCTACCTAGAAAGATCTTTAAGTGGTTCTCAACAAGCTTCATACGCAATGTAA
ATTGTATTATCTCTCAGGATGTGTGAGAACATCTGTTTTTCTTCTAATGCAGTAAACATATAAGGGTCT
CTTGGGATATCTTTTAAATAGACTTAATACAACATTCAGGAATGATAACAAAATATAATCAC
R
GTTGTAAGGGAATGTGAGCATTTCATATTAATAACATTGGAACCTTATGTTTAATACAGTGTTAAAAGT
TGACAAACATGTAGGAGTCAGAAAATTCAATTAAAATTATCACAGTAATATGAATTTAGCCACATCCTG
TGTTAGTTATGAAATCCATTTAACACCACAAACAGTAATATTTTTAGCCAGTTTATTCAAAA

FLA278845 (K = G/T) (SEQ ID NO: 417)
TCCATTTAACACCACAAACAGTAATATTTTTAGCCAGTTTATTCAAAAGGAAAACAGGAACTAAACCAC
TTTCATGCAATATATACTCTGTTAATGTGGTCAGGCTAATTTTGCTGGGGGAAGGAACTTAACTTTTGA
ATATTTGAATGCCCAGTCATTTAATCTGAATATCCTATTTCCTTGCATGTTGCAAAATTTTT
K
TCAATAAAAGGCAGAAAAAGAAATCTCTTCTCCATGCTCATCCCTAAGAGAATGGGTTGTCTGTACCCT
GAGAGCATTTTATGGAGGGGACAACCACTTTTCTAATTTTCCTTCCCACTTCTCTGTGGGCACAAATGC
TCTTTGGTTGAAAGAGTTGTAATTCAGTCCCAAGATGAGGTGTGGTTACTGCATCCCTAACC

FIG. 7 D

FLA280183 (R = G/A) (SEQ ID NO: 418)
ACAACACTTCCTCTGGTAAGATTTTCCTGACATCCTCTATAAAAAAAGATTGAGATAGTTGACTACCCA
AAATGTTTCCCATTCATTCCAAGCTCTATTCAAGGCAGTAAAGTGCCCGGCTGACAGATTGCATTCCTC
ATCTTTTCTGAAGCTAGCAATGGCCATGCAACAGCATTCTGGCCAATAAGATAGAAGTCGAA
R
TTGAAGGGTGGGATTTCCAAGAAAGCTCGTTGAAGACATAATTCCTCATTTCACTTCTTACTCTTTCTC
TTTCCTGCTTCCTAAAATGCGGTGCAGATGGCAGACACTTCAAAGCTGTCTCAGGCAATCAGGTGATGT
TAAGGCAGAAACCAGCTTTATGATGGGTAGAACAGGAAGAAAGAAGGCACCTATGTTCTTGT

FLA280923 (M = C/A) (SEQ ID NO: 419)
TCCCTACAAATCTCATGTTGACATTTTATCCCTAATATTGGAGGCAGGGCCTAGTAGGAGGTGTTTTGG
TCATAGTGATAAATGGCTTGGTGCCGTTCTCACAGTAACGAGTGAGTTTTTATTCTAGTGGTTCCTGCA
AGAACTGATTGTTAAAAGAGCTTGGATCCTTCCACCCCTCTCTCACTCTTGCTTCCTCTCTC
M
CACCTTGTAATCTCTACAAGCTCTTCACCTCCCCTTCTCCTTTTGCCATAAGTGGAAGATTTCTGAGGC
CTCACCAGAAGCAGATGTTGGTTCCATGCTTCTTGTACAGCCTGCAGAACCATGAGCCAAATCAACTTC
TTTTCTTTATAATTATCCAGTCTCAGGTATTCCTTTATAGCAACACAAATGGACTAAGACAG

FLA283400 (S = G/C) (SEQ ID NO: 420)
TGTCCGTGAGTTACAGATCTACACAAAATCACAGAGAGTGGTTAATCGTTTAGTCTGATGGTCAGGGAC
TTCCAAGAGACATGATTAGAAAACTGGTGACAAGGAGTCCTGGGGAAGAGGCATATGGATACCTCTGAA
CACACACAAAACATGAGAATATGTATCCCATATGAATGTTAACCAAAGAGCAGCCACAACAG
S
AAGAGGATTTTAAAATCAGCTGAATAAGATGATTCATTCTGACAGCATCAGCTAGTCTCTTTCCCCAGC
CACTGTTGCCCAGTGGGCTTACATATATCATGGCCATGGGGGCAGGGCTATGTATGGACACAGCAACAT
GAATTTCCACTCATCAAGGCCAATTTGGCTCCAGCCATTGCTGAGTGCTCAGCCTGCCAAGA

FLA283477 / SG13S25 (R = G/A) (SEQ ID NO: 421)
AGACATGATTAGAAAACTGGTGACAAGGAGTCCTGGGGAAGAGGCATATGGATACCTCTGAACACACAC
AAAACATGAGAATATGTATCCCATATGAATGTTAACCAAAGAGCAGCCACAACAGAAGAGGATTTTAAA
ATCAGCTGAATAAGATGATTCATTCTGACAGCATCAGCTAGTCTCTTTCCCCAGCCACTGTT
R
CCCAGTGGGCTTACATATATCATGGCCATGGGGGCAGGGCTATGTATGGACACAGCAACATGAATTTCC
ACTCATCAAGGCCAATTTGGCTCCAGCCATTGCTGAGTGCTCAGCCTGCCAAGATAGAAATCTACGCCA
ATATGGCACCATTCCCTGGGCTAGAAAACCAACTGGTGGAAGGTTGATTACATTGGACCATT

FLA284410 (R = G/A) (SEQ ID NO: 422)
CAGGGAATACAATGGTGGTTCCACTAAACTGACAGCTGAGTTTGCCATCTCCTCGTGCCAGTGAATACA
CAAGCAAGGAAGGGGGTTCCTTTCTCACCTAGGGTGACTGATCCTAATTACCAAGGAGAAATTGGACTG
CCACTTCACAATGAGGGTGAGGAGTATGTACTCTATGTGTCTGTGATTAATGTCAATAGAAA
R
TGACACCAACCTAGTACACAGAGGACTGATCATGGTCCAGGCCCTTCAGGAATGAAGATTTGAGTCACC
AGGCAAGGAACTTGGACTCACTGAGGAGGGCATATTCCAAGGAGAATATTTTATCTATGTCCATCTATG
TCCATCTATATTCCATCTGTGTTCCCCTTGGAATTCCTATTCATGAACATGGGGAATTCCAA

FLA284815 (M = C/A) (SEQ ID NO: 423)
AATATAGAATGAGTAGTGGAAGGTAGTTATAAATGTAAGTCAAAAACCACACAACCAATTTGAGAAATG
AGGAAGGTAATAGTGTTGAATATGTCTTCTTTATCTTGATATAAATGTATTTGTGCATATATTAACCAG
TTTATTTATTTATTATTATTTTTTGAGATGAGCTCTCGCCATGTTGCCCAGGCTGGTCTTGA
M
CTCCTGGGCTCAACTGATTCTACCATTTAGTCCTCCGAGTAGCTGGGACTACAGGCATGCACCACCATA
CCCAGCTGACCAGTTTTTTCCTATTCCTCTACTTAATTTCTCTACTATACAACATAATATGTGTTAATG
GTAGTTAACTTTATATCTCAGTATTAAGTCACAAGATATCAAAAAGGGAATGCGACTTAGTT

FLA284903 (Y = C/T) (SEQ ID NO: 424)
ATATGTCTTCTTTATCTTGATATAAATGTATTTGTGCATATATTAACCAGTTTATTTATTTATTATTAT
TTTTTGAGATGAGCTCTCGCCATGTTGCCCAGGCTGGTCTTGAACTCCTGGGCTCAACTGATTCTACCA
TTTAGTCCTCCGAGTAGCTGGGACTACAGGCATGCACCACCATACCCAGCTGACCAGTTTTT
Y

FIG. 7 E

CCTATTCCTCTACTTAATTTCTCTACTATACAACATAATATGTGTTAATGGTAGTTAACTTTATATCTC
AGTATTAAGTCACAAGATATCAAAAAGGGAATGCGACTTAGTTACAAGCAGAATGAATATCACTCAAAG
ATGAATAAAGAGAAGAGGGTTAGTGCATTTTCTGTTGGATGAGAGAAAGTTTCATTGTTAGG

FLA290195 (R = G/A) (SEQ ID NO: 425)
TCTTTTTGTTCTGTCTCAGCAGCTCTCTATTAAGATGAATGGCATTTCCAAAGGCTTCACCTCTGATAA
GTGTTCCTCTGCAGCTGCAGCCAGAATCTTAATGTGCGCGCTGTAATTTAATGGCCGTCTCGGCTATTA
ACACGCTCTTCTCGGGTGAAGTGGACTCCCTCCATCCCCGGGCCTCTGCACGTGCTCTGCGC
R
CTGGCTGGGGGTGACTCCAAGGAGCTCAGAGCGGGGTGCCCGGCACCTCTCGCCAGGCGCCTTTCGACC
TTCTAAAGCGCGAATGGCTGGACTTTTCTCCCATGTGTGGGGCCCCAGAAGGTGTGGGGCCCCAGAAGG
TGTGGGGTCCCTGCGTTCCACGGAGCCCGGAAGGTTTCCAGTGATGGTGGGGGCTGACCACG

FLA290553 (S = G/C) (SEQ ID NO: 426)
ACGGAGCCCGGAAGGTTTCCAGTGATGGTGGGGGCTGACCACGTTGGTCCCCGTGGGTGCTGTTTTCAT
GTGCCGGCAGATTGGGATGAGTTTAAAAGACAGAAGCGTGTAGGATAGAGAAACTTCTTTAAAAACTGG
AAATTTTAATCTGGGGATTATAACTATTGGACAGTCAAGTGCAAGAGTGAATACACTTCTCA
S
TCCCTCCTCCCAATTTTTATTTGCGGGATTAGTCAGTCCCCCTCTGCCACATGATAATTGTGAGAACTA
CCAGGGTCTTCATTCTCCTGCCATCTGGTTGACCTCTCCAAGAATGGACACCCGGGCAGCCTGGGCCAA
TGAGGCTGTCCTAAGAGTTTAGATGAGAGAAGTCAGTCTTTGACAGGTGATGGAAGCTGTAA

FLA290570 (Y = C/T) (SEQ ID NO: 427)
TCCAGTGATGGTGGGGGCTGACCACGTTGGTCCCCGTGGGTGCTGTTTTCATGTGCCGGCAGATTGGGA
TGAGTTTAAAAGACAGAAGCGTGTAGGATAGAGAAACTTCTTTAAAAACTGGAAATTTTAATCTGGGGA
TTATAACTATTGGACAGTCAAGTGCAAGAGTGAATACACTTCTCACTCCCTCCTCCCAATTT
Y
TATTTGCGGGATTAGTCAGTCCCCCTCTGCCACATGATAATTGTGAGAACTACCAGGGTCTTCATTCTC
CTGCCATCTGGTTGACCTCTCCAAGAATGGACACCCGGGCAGCCTGGGCCAATGAGGCTGTCCTAAGAG
TTTAGATGAGAGAAGTCAGTCTTTGACAGGTGATGGAAGCTGTAAAATGTAAAACTCCACAG

FLA292253 (K = G/T) (SEQ ID NO: 428)
TCTCCACCAGCAGCTTTTCTGAGTCTCCAGCTTGCAGATGGCAAACCATGAAACTTCATGGTGTCCATG
AGCATGTGAACCAATTTCTATTATAAATCTGCAATATATATATATGAGGAGACTTATTTATATATTGGT
TCAGTTTCTCTGGAGAGCCTTGGCTAATATAAAGTCTATACTCTACAAAGTGCCCTAGGTAC
K
CAGGGAGTACCCAAGTGTGTCATGACCAGCCCGACAGCCCTGGCTGCTGGCTTCCCCGCACACAACTCT
GCACGCTGCCTTCATCAGCCTTTCTCTCTCAGCTGAACCGAGGGCATTGAAGCGGGCCTCTGGCACTGT
ACCTATGAGGGAGCAATATCTTCCCCTACACTGACCTCTTCCGTGCCGAGATGCAGCCCTCC

FLA292576 (W = T/A) (SEQ ID NO: 429)
GGGCCTCTGGCACTGTACCTATGAGGGAGCAATATCTTCCCCTACACTGACCTCTTCCGTGCCGAGATG
CAGCCCTCCCTGCTGCCACTAGTTACAGTGGTCCATGTTCCCTTTCAAAGTGAAGTTTTGATAAAAGCA
CCTCTTAACCAATGCCAAATAGCTAAGTCTGGGACAAAGATTGCAGGTATTTTGCATTTTCC
W
TGTAACCTCAGAGGGATTGCCATTCACACTGATCTGAGCTGCAGAATACCAGGCAGCCACCTCACCCAC
CCAGCAGGTCCACTCTTATACTTTCTCAGAAAGCACAGCCACTCTACTCTTATTCAGTTGAAAAGAATT
TCCAGGAAGGTGTTTCTGCGATTGCCTCAGAAAAGTCAGTTCCCTTTGGGAATTTCCCTTAG

FLA295036 (R = G/A) (SEQ ID NO: 430)
CATTTTTATACTAAATTACACACAACAAAGTTGTAGCTCAGAGAGGGAACAAATGGCTTATTTAGGCCA
CCATTTTCTTGAGCCATTATGATTTCACACAGGGCTCCCTTGGCCCTGTAAATTGGCAAGGATTCCATT
ATTCAACCCGCATACATGTACAGAGACCCTGCTCTGGCCCAGATAGTATTCTGGGTACAGGC
R
GATAGAGCAGGAAACAAAACAGCTACAGTGATGGACAGGTCAGCCTGCAGCAATGCCTGCAGTCTCTGC
AAAGGTAGCTGTATGGGTGGGCAGGTGGCTAGCACTTATTCAGCTCTGGAAGGATCTCCCCTCTGGCCT
CTCCCCTGACACCCATCAATAAAACTGAGGAGCATCGGTGGACAGGGGACCTTGTGCCCCCT

FLA296102 (W = T/A) (SEQ ID NO: 431)

FIG. 7 F

GGAGGGGGCAAAACATTCAAATAACTCAGGAGATAACACAACTATTTGTTTTTAACTGTGAGTTTTTAG
GCAATCACAAAGATCCAGATGTATGTCCAAGCCTCTCTTTGCAATTCTAATTAACCTCAATGTTGCAAC
CATAGACCTACCTTACAGAGTTCAAAAAAATATGCAAAAACCCTGCCTTTCTTCTTCCTCAT
W
CCCCAAAATGCCATTCTGAACATTTCCTGTTAGTTAAAAAAAGATTTCCATGGTGTTACCAGGCACTGT
ACACAGTCTGTGTCCCAAGACAAGGAGGTACAGTTCCACATGCGCCCATGACTGGGTTGGGCTCTGCAC
TCTCTCTATACTTTGAGAGCCTGATTTTCTGTGATTGGGCAGAGCTGGCCCACCTGGTGCAA

FLA298098 (R = G/A) (SEQ ID NO: 432)
AATCATCTGACTTTAGAGAGTAGACACTTGCTCCATGCATATTGCCTCCAATTCATTCATTCAAGCACT
CCCTGCTCAAGAAGTTCTTTCTTATGTTGAGCTGAAATCTGCAGCCCTATGCGTTTTACCCAGCAGTCC
TGGTGCTGTTCCCTAAAATCACTTAGACTGTGCCTGCTCTTTCTGTGTTTACAGTGTCAGCT
R
TAATATCCCCCTCTTCGGCCTAACGTTTCTGAAGTCCCTTGCCACTGGGTCTCCTCTCCTCTTCCTGTG
TTCTTTCTAAGAACACCTATGCAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCTGAGATCCGGGCAT
CGACTCTGTTAGAATAATCTACGTATGAGTTATTTTTTTGAGAACTATGTGTCATTGCTGAC

FLA298188 (R = G/A) (SEQ ID NO: 433)
TTATGTTGAGCTGAAATCTGCAGCCCTATGCGTTTTACCCAGCAGTCCTGGTGCTGTTCCCTAAAATCA
CTTAGACTGTGCCTGCTCTTTCTGTGTTTACAGTGTCAGCTGTAATATCCCCCTCTTCGGCCTAACGTT
TCTGAAGTCCCTTGCCACTGGGTCTCCTCTCCTCTTCCTGTGTTCTTTCTAAGAACACCTAT
R
CAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCTGAGATCCGGGCATCGACTCTGTTAGAATAATCTA
CGTATGAGTTATTTTTTTGAGAACTATGTGTCATTGCTGACTCATATTAACTCTGTGGTTAACTAAAAT
CTCAAGATCTCTTTATGTTTGTTGAGAAACTTATTTAACTTCTCTGGCCCTCCGTTTCCTTC

FLA298230 (Y = C/T) (SEQ ID NO: 434)
CAGTCCTGGTGCTGTTCCCTAAAATCACTTAGACTGTGCCTGCTCTTTCTGTGTTTACAGTGTCAGCTG
TAATATCCCCCTCTTCGGCCTAACGTTTCTGAAGTCCCTTGCCACTGGGTCTCCTCTCCTCTTCCTGTG
TTCTTTCTAAGAACACCTATGCAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCTGAGATC
Y
GGGCATCGACTCTGTTAGAATAATCTACGTATGAGTTATTTTTTTGAGAACTATGTGTCATTGCTGACT
CATATTAACTCTGTGGTTAACTAAAATCTCAAGATCTCTTTATGTTTGTTGAGAAACTTATTTAACTTC
TCTGGCCCTCCGTTTCCTTCACTGAGCAGTGGAGTGATTGATAACCTCCACCTGTGGTTGCT

FLA298379 (M = C/A) (SEQ ID NO: 435)
AACACCTATGCAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCTGAGATCCGGGCATCGACTCTGTTA
GAATAATCTACGTATGAGTTATTTTTTTGAGAACTATGTGTCATTGCTGACTCATATTAACTCTGTGGT
TAACTAAAATCTCAAGATCTCTTTATGTTTGTTGAGAAACTTATTTAACTTCTCTGGCCCTC
M
GTTTCCTTCACTGAGCAGTGGAGTGATTGATAACCTCCACCTGTGGTTGCTGAAGGTCTTGCACAAGAT
GATATAGTTAAAGTAGCTAGCAGTGCCCACGTACGGCGGATGCCTCACAACGGTTTGCAGCCATCTCTC
TATCTGTGTCTTTGTCTCTCTCTCACACTGGTTTTGGCTTACTGTTAGCAGCTAGCCGAGAT

FLA298507 (M = C/A) (SEQ ID NO: 436)
ACTCTGTGGTTAACTAAAATCTCAAGATCTCTTTATGTTTGTTGAGAAACTTATTTAACTTCTCTGGCC
CTCCGTTTCCTTCACTGAGCAGTGGAGTGATTGATAACCTCCACCTGTGGTTGCTGAAGGTCTTGCACA
AGATGATATAGTTAAAGTAGCTAGCAGTGCCCACGTACGGCGGATGCCTCACAACGGTTTGC
M
GCCATCTCTCTATCTGTGTCTTTGTCTCTCTCTCACACTGGTTTTGGCTTACTGTTAGCAGCTAGCCGA
GATAAGTGTGTTTATGGTCTTTGCATGTATTGTTTCTGTAGCATACTGGAGGATTACAAGAGGTTGGGG
AGTGAGGGGGCGGTGAGGAGTAGACAAAGGCAGCCAACTCTTCCAAGTTTAGCTTAGAAGGA

FLA298604 (Y = C/T) (SEQ ID NO: 437)
GATTGATAACCTCCACCTGTGGTTGCTGAAGGTCTTGCACAAGATGATATAGTTAAAGTAGCTAGCAGT
GCCCACGTACGGCGGATGCCTCACAACGGTTTGCAGCCATCTCTCTATCTGTGTCTTTGTCTCTCTCTC
ACACTGGTTTTGGCTTACTGTTAGCAGCTAGCCGAGATAAGTGTGTTTATGGTCTTTGCATG
Y
ATTGTTTCTGTAGCATACTGGAGGATTACAAGAGGTTGGGGAGTGAGGGGGCGGTGAGGAGTAGACAAA
GGCAGCCAACTCTTCCAAGTTTAGCTTAGAAGGAAGGAGCGGTAAACCCTAGTTGAATGTTGGACTGAA
GCAGGTTTGTTTTTGTTTTGTTTAAAGGATAGGGAAGATCTGTGCGTGTTTCCAGGATAAAG

FIG. 7G

FLA298987 (Y = C/T) (SEQ ID NO: 438)
CGTGTTTCCAGGATAAAGAAAAGGAGAGAATATGATATTAAAGATTCTGGAAGTGGGAGAAGGAGCAAT
GAAATACAGACTTGAAGTCAGTGGCATGGACAGGGTCAAGATCACAGTTAGAGGATGCAGCCTTAGAGA
AAAGGAAGGGGCTCGGTTCTCTGAGCAAGGAGGGAAAGAAGAGAGGCAGATGCAGAGAAGTA
Y
GGCACATCGTGCTGCTGGTTGTAGAAATAACCTCTGACTTTTAATAAAGTCATCCCTCGGTATCCCTGG
GGGATTAGTTCTATGACCTCCCTCGGATGCCAAAATTCGTGGATGCTCAAGTCCCTGATATAAAATGGC
ATAGTATTTGCATTTAACCTACACACATCCTCCATATCCTTTTTTTTTTTTTTTTTTTTTTT

FLA299063 (R = G/A) (SEQ ID NO: 439)
AGACTTGAAGTCAGTGGCATGGACAGGGTCAAGATCACAGTTAGAGGATGCAGCCTTAGAGAAAAGGAA
GGGGCTCGGTTCTCTGAGCAAGGAGGGAAAGAAGAGAGGCAGATGCAGAGAAGTACGGCACATCGTGCT
GCTGGTTGTAGAAATAACCTCTGACTTTTAATAAAGTCATCCCTCGGTATCCCTGGGGGGATT
R
GTTCTATGACCTCCCTCGGATGCCAAAATTCGTGGATGCTCAAGTCCCTGATATAAAATGGCATAGTAT
TTGCATTTAACCTACACACATCCTCCATATCCTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGT
GAGATGGAGTCTTGCTCTGTCGCCCTGGCTGGAGTACAGTGGCTCGATCTTGGCTCACTGCA

FLA299772 (S = G/C) (SEQ ID NO: 440)
CTCAGCCTCCTGTGTAGCTAGGATTACAGGCCCCTCCCCACCCCCACCCCCCAACAACTGGCTAATTTT
TGTATTTTTAGTAGAGATGGGGTGTCACCACGTTGGCCTGGCTGGTCTTGAACTCCTGACCTCAGGTGA
TCTACCCGCTTCAGCCTCCCAAAGTGATGGGATTATAGGCATGAGCCACTGTGTGTGGCCTA
S
ATTACTTATAATACCTGATAGAATGTAAATGCTATGTAAACAGTTGTTATACTGTATTGTTAAAAGACA
GTAACAAGAAAAAAAATCTGTACATGTTCAGTCCAGACAAATGGTTTTCTGTTTTTTTTTTTTTTTTT
AATATTTTTGGTCAGTGGTTGGTTGACTCCAGGAATGCAGAACCCGCAGATATAGAAGGTTG

FLA299843 (Y = C/T) (SEQ ID NO: 441)
TATTTTAGTAGAGATGGGGTGTCACCACGTTGGCCTGGCTGGTCTTGAACTCCTGACCTCAGGTGATC
TACCCGCTTCAGCCTCCCAAAGTGATGGGATTATAGGCATGAGCCACTGTGTGTGGCCTAGATTACTTA
TAATACCTGATAGAATGTAAATGCTATGTAAACAGTTGTTATACTGTATTGTTAAAAGACAG
Y
AACAAGAAAAAAAAATCTGTACATGTTCAGTCCAGACAAATGGTTTTCTGTTTTTTTTTTTTTTTTTAA
TATTTTTGGTCAGTGGTTGGTTGACTCCAGGAATGCAGAACCCGCAGATATAGAAGGTTGATTATGCGT
TCAGAGGCAGGGAATACCATCTTGGGTTCCAGAAAGAAAATGATCAGCATTTTCTGTCATAC

FLA299980 (R = G/A) (SEQ ID NO: 442)
ATAATACCTGATAGAATGTAAATGCTATGTAAACAGTTGTTATACTGTATTGTTAAAAGACAGTAACAA
GAAAAAAAATCTGTACATGTTCAGTCCAGACAAATGGTTTTCTGTTTTTTTTTTTTTTTTTTAATATTT
TTGGTCAGTGGTTGGTTGACTCCAGGAATGCAGAACCCGCAGATATAGAAGGTTGATTATGC
R
TTCAGAGGCAGGGAATACCATCTTGGGTTCCAGAAAGAAAATGATCAGCATTTTCTGTCATACTCTGGT
AAAAACAGATCTTTTGAATGGACAGGTGTATTAAACCCTGTGGAGCTGGCTGGGCCTGGCGGCTCACGC
CTGTAATCCCAGCACTTTGGGAGGCTGAGGCAGGTGGATCACGAGGTCAGGAGTTCGAGACC

FLA300662 (R = G/A) (SEQ ID NO: 443)
TATGCCCCGCAGAGTTTGAAGTCCCGGCTGCACCTCTCCCCAGCAGCAGGTTGACTCTGGAAAGTTGCA
GCGTTCTTACCTACAGAGTGGGAACAGTACTACCCATTGCACAGAGTGGGTGCAAAGCTCTGTGACGGA
ATACATGGCAAGTGCCCACCACATTGCCTGGGATGAGGTGGGCCCTTCCTTTACGTAAGAGA
R
CCCTACAGATACACTCAAAGTGGGCACATTCCTACAGAAGGAGTGTTATTTGTGTAGAAAAGAAAAACA
TGAAAGGCTTTTATTCCTATACACAATAAAGCACCCCTTTAATGTCTTTTTGAGGAGGATAATATGAAA
TTGATGAAAAGGAACCCTGTGGTTGGATCCCTGACAATCACATGTATCCCTTTTTTCACTCT

FLA300864 (R = G/A) (SEQ ID NO: 444)
CCTACAGATACACTCAAAGTGGGCACATTCCTACAGAAGGAGTGTTATTTGTGTAGAAAAGAAAAACAT
GAAAGGCTTTTATTCCTATACACAATAAAGCACCCCTTTAATGTCTTTTTGAGGAGGATAATATGAAAT
TGATGAAAAGGAACCCTGTGGTTGGATCCCTGACAATCACATGTATCCCTTTTTTCACTCTT
R

FIG. 7 H

AAAAAGGAGTAAAGGAATAAAATAGAAGGGGAGAGGGGGCAGAGAGACCTTCACCGCCCCCCCCCCACC
CCCCATCATCCAATCTATAGTCAAACCCTCCAGACTGTGTCTCCTTGGCATCTCTGACACCCCCACCGC
CACCACCCCAGTCAATTCCTATCTTATCCCCCTATCCTGGATCTGATTCTGCTAAGTTCCTG

FLA302094 (R = G/A) (SEQ ID NO: 445)
GAACATTCTGAACCACAGACAGTTCTTTACCCTGAACCTTTGCATATTTTGTTCTCTTAGCTTAGAGCG
GCCCCTCTCCCTCCGTCTGCTTGGCTAATTTCTACTTGTTCTTCAGATTTTATCTTAGATGTCATTCCC
TCAAGGAATCCTTCTGTGACTCAACATGGAATTAAGTTGCCTCCTTTGACCCTGAAAGCACC
R
TGTACTCAATCTCATCTTGGCATGACTCACTTTGCTGTGTGGAATGTCTGCTTTCCTTGTTTGTCTATT
CCTTTAGACTGTAAGATCCTAGAAAGTGGGGGCCGTGCCTTGCTCATGACTGTGTTTCTAACACCAAAC
ACAGTGTTCAGTAGAGAGCAGCTGCTGAGTACGTTTCTGCTAAATGACAGTTGATGGAGGAC

FLA303769 (W = T/A) (SEQ ID NO: 446)
TCATCTAGGTATTTTTAATTGTTTCAGTGAGGTGTAGGCATGAGGGGATTGGAGGGGGCATCTCCTCCA
TTGCAGTTTTTCATTGGCTGCTTTGCTCCCTCAGCTCCGAAATCGCTGGGCCACTCTCGAACGCATTAG
TACGGTAGTCACAGGTTGATTGCCTGGCCCCTTGCCCTCTGTGGGCATTTTCCCTTTCAGAC
W
GCCCCTGAGTACTCACAGTGCTGCTACAGTGGGCCACCTAGATCTCCCTCTTTCTCCATGCTCCCACGT
GCTCTGGGCTCCACTCCCTTCTCCCAAGCACTTCTGTCCAGGGCTATTCCAGCAGTCTGACCTCAAGGA
AATCCTTTGCTAAACTGATTATAGAGAGGTTTCTATTTTAACATTTAGGTCTTCCATGTATT

FLA303796 (Y = C/T) (SEQ ID NO: 447)
TGAGGTGTAGGCATGAGGGGATTGGAGGGGGCATCTCCTCCATTGCAGTTTTTCATTGGCTGCTTTGCT
CCCTCAGCTCCGAAATCGCTGGGCCACTCTCGAACGCATTAGTACGGTAGTCACAGGTTGATTGCCTGG
CCCCTTGCCCTCTGTGGGCATTTTCCCTTTCAGACAGCCCCTGAGTACTCACAGTGCTGCTA
Y
AGTGGGCCACCTAGATCTCCCTCTTTCTCCATGCTCCCACGTGCTCTGGGCTCCACTCCCTTCTCCCAA
GCACTTCTGTCCAGGGCTATTCCAGCAGTCTGACCTCAAGGAAATCCTTTGCTAAACTGATTATAGAGA
GGTTTCTATTTTAACATTTAGGTCTTCCATGTATTAATTCTCAGAATCAATTTAAGATGTTT

FLA303957 (Y = C/T) (SEQ ID NO: 448)
TCCCTTTCAGACAGCCCCTGAGTACTCACAGTGCTGCTACAGTGGGCCACCTAGATCTCCCTCTTTCTC
CATGCTCCCACGTGCTCTGGGCTCCACTCCCTTCTCCCAAGCACTTCTGTCCAGGGCTATTCCAGCAGT
CTGACCTCAAGGAAATCCTTTGCTAAACTGATTATAGAGAGGTTTCTATTTTAACATTTAGG
Y
CTTCCATGTATTAATTCTCAGAATCAATTTAAGATGTTTAAAGGTGTGATTTAAGACATTTTAAAACCA
TTTGGAGGAGAGTACAGAAATTATGTCACTTGCTGTCAGCCTCTTTGCACCATCTGCAGAGAAAGATAC
TAGAGTCCCGCCTTGGACACATCCACATGCAAGAGGTGCAAAGAAGGTGTCTTTGATGAGGC

FLA303967 (W = T/A) (SEQ ID NO: 449)
ACAGCCCCTGAGTACTCACAGTGCTGCTACAGTGGGCCACCTAGATCTCCCTCTTTCTCCATGCTCCCA
CGTGCTCTGGGCTCCACTCCCTTCTCCCAAGCACTTCTGTCCAGGGCTATTCCAGCAGTCTGACCTCAA
GGAAATCCTTTGCTAAACTGATTATAGAGAGGTTTCTATTTTAACATTTAGGTCTTCCATGT
W
TTAATTCTCAGAATCAATTTAAGATGTTTAAAGGTGTGATTTAAGACATTTTAAAACCATTTGGAGGAG
AGTACAGAAATTATGTCACTTGCTGTCAGCCTCTTTGCACCATCTGCAGAGAAAGATACTAGAGTCCCG
CCTTGGACACATCCACATGCAAGAGGTGCAAAGAAGGTGTCTTTGATGAGGCAAGGTCAAAA

FLA304170 (Y = C/T) (SEQ ID NO: 450)
ATTCTCAGAATCAATTTAAGATGTTTAAAGGTGTGATTTAAGACATTTTAAAACCATTTGGAGGAGAGT
ACAGAAATTATGTCACTTGCTGTCAGCCTCTTTGCACCATCTGCAGAGAAAGATACTAGAGTCCCGCCT
TGGACACATCCACATGCAAGAGGTGCAAAGAAGGTGTCTTTGATGAGGCAAGGTCAAAACTT
Y
CTCCCCAGACGAAATCCAAAGAAAGCATTCCTACTATGCTATATCAGTTTGGAAAGAAAAACTTCTGCC
AGGTGACTGCATTCTCACTGGTCACATTGTGTTCCTATGGACTCCTCAGCTCAACCAATTTGGAGAAGT
TATGGTGCAATTTCACCATATCTGGTTAGAAGTTAAGTTTCCAATTTGCTGGCAATGAAGAA

FLA304334 (Y = C/T) (SEQ ID NO: 451)

FIG. 7 I

CAAAGAAGGTGTCTTTGATGAGGCAAGGTCAAAACTTCTCCCCAGACGAAATCCAAAGAAAGCATTCCT
ACTATGCTATATCAGTTTGGAAAGAAAAACTTCTGCCAGGTGACTGCATTCTCACTGGTCACATTGTGT
TCCTATGGACTCCTCAGCTCAACCAATTTGGAGAAGTTATGGTGCAATTTCACCATATCTGG
Y
TAGAAGTTAAGTTTCCAATTTGCTGGCAATGAAGAAGAAATGGAGCAGGCCAGGCTGTGTAGTTTCTGC
CACGTGCCCCCGGGAGTGAACAGCTCTGTTTGTAAGAAGCCATGGTGCTTAGACCTGGGCTCGCTAGTT
GCCAGCCTCCAAATTGCAGAAGTGCCCTTTGGTTGGTGGCTATGCTGTGTCACTTGGGAAGG

FLA304512 (Y = C/T) (SEQ ID NO: 452)
GGTGCAATTTCACCATATCTGGTTAGAAGTTAAGTTTCCAATTTGCTGGCAATGAAGAAGAAATGGAGC
AGGCCAGGCTGTGTAGTTTCTGCCACGTGCCCCCGGGAGTGAACAGCTCTGTTTGTAAGAAGCCATGGT
GCTTAGACCTGGGCTCGCTAGTTGCCAGCCTCCAAATTGCAGAAGTGCCCTTTGGTTGGTGG
Y
TATGCTGTGTCACTTGGGAAGGTCGTTTGGAAGTTCCACAGTCGTTGTGGGGTGCCAGAGATTAAAAAG
CGTAAGAGGAGAGTGGAAAGTGATTGTTGCTGCTTGGGCATCCCCACCGTGTGGGTGCTGCAGCCCAGC
TCTCAAAACCCATGGGTCTGTACACTCAACCTCCATGAGAGGGAAGGAGAAGGATGAGGGAG

FLA304583 (R = G/A) (SEQ ID NO: 453)
GCCAGGCTGTGTAGTTTCTGCCACGTGCCCCCGGGAGTGAACAGCTCTGTTTGTAAGAAGCCATGGTGC
TTAGACCTGGGCTCGCTAGTTGCCAGCCTCCAAATTGCAGAAGTGCCCTTTGGTTGGTGGCTATGCTGT
GTCACTTGGGAAGGTCGTTTGGAAGTTCCACAGTCGTTGTGGGGTGCCAGAGATTAAAAAGC
R
TAAGAGGAGAGTGGAAAGTGATTGTTGCTGCTTGGGCATCCCCACCGTGTGGGTGCTGCAGCCCAGCTC
TCAAAACCCATGGGTCTGTACACTCAACCTCCATGAGAGGGAAGGAGAAGGATGAGGGAGGGGAGAGAT
AGCCATGGAAAGGTAGGAACTAAGCAGGCAGGGTGGAGAGTTTTCTGTAAGACAAAAACTGT

FLA305089 (R = G/A) (SEQ ID NO: 454)
GGCAGCTACATGCTGGCAAAAGCCAGAGGCAGCTGGTCTGTTTGCCTGTGCCAGGAAACCACTGGGAAT
GGGGTTGTGTGTTATTCTAGGAGAAAGTCGTCCCAGCAGCAGCTTCTCCAGGGGCATCCAAGAGCACTG
AAAAGGGTTGCAAGATGACCCATGAGGCTGCAGGAAGAAAAGAACATGCATTTAATCTTGCT
R
TCTGAAAAGTAAGACATGAAGCTTTCCTCATTTTTAATATACACATGGACAGTAGTATGTGTATATAGT
TTATATGCAAATATACTTGTTATAAGGTTGCATGCTCAAAATTTTTGGTTCATGGGGTGTGGGATCATA
AATGTTTAGGGACCATGGCTATCAAGGAAAAACAGCATGAAGGATAAATGATACTGGTGGAT

FLA305505 (W = T/A) (SEQ ID NO: 455)
ATGTATTTTTAGCATAAAACACAACTGCTGACTGATACAGATAGCTCAAGATTCTGGGGCAGCTGCTGA
ACAGATACACTAGCCAGTGTGGCTCATCGGCTCAGACTTGGCCTTAATTAATGGGCTGTCCCTCCACCC
ATCTCCCATGAGGGCAGAGCTGAGCCAGGGTTTGAGAGCTAAAAGGAATTGGACCTGGACTC
W
GTTCACGTGTATATTTTAATTCTAATTAATTCATTCTTTTGAAAGACAGAGTCACACTCTGTTGCCTAG
GCTGGAGTGCAGTGGCACGATCTTGGCTCACTGCAACCTCGGCCTCCCAGGTTCAAGTTATTCTCCTGC
TTCAGCCTCCTGAGTAGCTGGGATTATAGGCACATGCCCCCATGCCTGACTAATTTTTGTAT

FLA305678 (Y = C/T) (SEQ ID NO: 456)
GAGCTAAAAGGAATTGGACCTGGACTCTGTTCACGTGTATATTTTAATTCTAATTAATTCATTCTTTTG
AAAGACAGAGTCACACTCTGTTGCCTAGGCTGGAGTGCAGTGGCACGATCTTGGCTCACTGCAACCTCG
GCCTCCCAGGTTCAAGTTATTCTCCTGCTTCAGCCTCCTGAGTAGCTGGGATTATAGGCACA
Y
GCCCCCATGCCTGACTAATTTTTGTATTTTTAGTAGAGACGGGGTTTCACCATGTCAGGCTGGTCTTGA
ACTCCTGACCTCAGGTTATCCACCCGCCTTGGCCCCTCAAAGTGTTGGAATTACAGGTGTGAGCCACCG
TGCCTGGCCTGTTCACATGTATAAAACACAGTTTAATGTCCTATTCCCAGCCAATGAGCATG

FLA305956 (K = G/T) (SEQ ID NO: 457)
CCTCAGGTTATCCACCCGCCTTGGCCCCTCAAAGTGTTGGAATTACAGGTGTGAGCCACCGTGCCTGGC
CTGTTCACATGTATAAAACACAGTTTAATGTCCTATTCCCAGCCAATGAGCATGGCTAGAGCAGCCTTG
GTCAAAGTTTGGTTTTTGGAGAAAAATCCTTGTTAGCTGACCTAAGATTCCTCTTTGTGAGT
K
TAAGTAAGCACAGGTTGCAGAGAGGAGAAGGGTCTCTGGAGAGGTGTAATTTTCTAAATGGATTACAAG
TTCATGGACTTTTAACAGGTGTTACAGGGGATAACAAGTTCTTTATAGACAGACTTTTGAGGACGTTTA
AGGGTATTCTGATTCTTGGTTTTCTAAGAGGGGAATGTATTATTTAACTACAGACACCCCTA

FIG. 7J

FLA306447 (Y = C/T) (SEQ ID NO: 458)
ATTCTAGACTCACTTTCTTTCTGTTTTTTATTTTTATTTTTTTTTGAGATGGAGCTTCACTCTGTCACC
AGGCTGGAGTGCAGTGGTGCAATCTTGGCTGACTGCAACCTCTGCCTTCCGGGCTTAAGCAATTTTTGT
GCCTCAGCCTCCTGAGTAGCTGGGATTACAGCATGCACCACCATGTCCGGCTAATTTTTGTA
Y
CTTTAGTAGAGACAGGGTTTCACTATGCTGGCCAGCCTGGTCTCAAACTCCTTACCTCAGGTGATCTGC
CCGCCTCGGCCTCCCAGAGTGCTCAGATTACAGACGTGAGCCACTGGTGCCTGGCCTAGACTCACTTTC
AAGTGGCATAGACTTGTAAAATTATTTAAAGGTGATAGGTCTACAATGATCCTGTCAATTAG

FLA307155 (Y = C/T) (SEQ ID NO: 459)
AGAAAATCCAGAATAATAATAATTTGTCAATAGGAAAGACATTTCCACTGGGGGTTAAGAAGGAAGACA
TTGGAACAATGATAGCCACCACTTATTGAATGCTTACTGTGAGCCAGGTGGCACTTCACCTTGTTTCAT
TCTCACAACAGTCTAGGGAAGTAATTACTAATGTCTCCATCCACCTCTTGTAGATGAGCAAA
Y
TGAGGCTCATTGAGGCTAGGAAATGCACCCACACTCACATAGCCCATAAGAGGCAGCCATGGCATTGGG
CCCAGACCATGTGAACTTCAAAGACTACACGAGCAGCCACTGGGCAGCTGTCATGGCTAAAGCCACTTG
AATTCAGCCCAGCAGCAACCCCCTCTCCAGGAGGGGCACATAAGCTTGCAGCTTTGGGTAGA

FLA307165 (Y = C/T) (SEQ ID NO: 460)
GAATAATAATAATTTGTCAATAGGAAAGACATTTCCACTGGGGGTTAAGAAGGAAGACATTGGAACAAT
GATAGCCACCACTTATTGAATGCTTACTGTGAGCCAGGTGGCACTTCACCTTGTTTCATTCTCACAACA
GTCTAGGGAAGTAATTACTAATGTCTCCATCCACCTCTTGTAGATGAGCAAACTGAGGCTCA
Y
TGAGGCTAGGAAATGCACCCACACTCACATAGCCCATAAGAGGCAGCCATGGCATTGGGCCCAGACCAT
GTGAACTTCAAAGACTACACGAGCAGCCACTGGGCAGCTGTCATGGCTAAAGCCACTTGAATTCAGCCC
AGCAGCAACCCCCTCTCCAGGAGGGGCACATAAGCTTGCAGCTTTGGGTAGAAGCTGCACTT

FLA308514 (K = G/T) (SEQ ID NO: 461)
GCAGTTTGAAAATTGCATCTTTGTTTTTACCTATATAATCACATGAAACCCGTGGTTCTCAAACGTCAG
CAGGCATCAGCATCACATGGAGGGCTTGTTAAAACAGATTTCTGGGCCCCAACACAGAGTTTTAAATTC
TGAAGGCCTGAGGTGGGTGTGAACATTTGCATTTCTAACATGTTCTCGATGCTGCTGCCGCC
K
CTGGTCCCGAGAGCATGCCTGGAGAACTGCCACCTTCGACCATGGACTGTGAGAATTCACATGGACCTC
AGAATTATAATCAGTCTCTCAGTTTTACAGATAAGGAAACTAAATCCAGAGAGATTGTTTTGCCAATGG
TGAACAGCTGGTTAAAGTCAGGATGGAGACTTTAATCCTAGTCAAGTGACCTTTCCTCTGTA

FLA308527 (K = G/T) (SEQ ID NO: 462)
TGCATCTTTGTTTTTACCTATATAATCACATGAAACCCGTGGTTCTCAAACGTCAGCAGGCATCAGCAT
CACATGGAGGGCTTGTTAAAACAGATTTCTGGGCCCCAACACAGAGTTTTAAATTCTGAAGGCCTGAGG
TGGGTGTGAACATTTGCATTTCTAACATGTTCTCGATGCTGCTGCCGCCTCTGGTCCCGAGA
K
CATGCCTGGAGAACTGCCACCTTCGACCATGGACTGTGAGAATTCACATGGACCTCAGAATTATAATCA
GTCTCTCAGTTTTACAGATAAGGAAACTAAATCCAGAGAGATTGTTTTGCCAATGGTGAACAGCTGGTT
AAAGTCAGGATGGAGACTTTAATCCTAGTCAAGTGACCTTTCCTCTGTATTTATTTCCCTCC

FLA309851 (R = G/A) (SEQ ID NO: 463)
GTGATCTGCCTGCCTCAGCCTCCCAAATTGCTGGGATTACAAGGCGTGTTGTTTTAAGCCACTCAGTTT
GTGGCCACTTGTTACAGCAGCAAGAGGAAACTCATACAGTTATCATGTGAACTCACAGGAATATGGTGA
GTTAAAAAGAGAGGAAGGGTGCAAAACATCCACGGTAGAGTGAGAACTCTCCAGGGAGTGAG
R
ACTGTGCCCAGCATACAGTGATCACCCTCTTAGTAAGCTAAGTTTCTGAGCACCAGCTTTTTTGAGTTG
ACTTTGTTGTCTTTAACATTTGAAGATCACCCTTCTTTGCTCAGCCTGGCTTGCAGACCTGGGCTGATT
TGTGGATCTGATAGAAAAGTTTCCTTAGTTGGGCTCTTCTCCCCGACCACCCCCATGCCAGT

FLA311122 (R = G/A) (SEQ ID NO: 464)
CCACAGTTATCAGCAGCCCACAGGCTTGACTTGAGCAAGTTGGAAAGACAAATCAACTTCCAGAGTTGA
TTTAACATTGAGTGGAAATCAGTCATACTTTTGGTCCCCTTTCGGGGCCACGCCTGGCACTGTGCCTGG
TGGCAGATCGGCATGAACTGGCCAGCTTCTGTGGCCCTGGAGGGCACAGGCAGAAAGGCCAC
R

FIG. 7K

CTCAGTCCCATGATGAACTGTTTAAGACTTATTGTTGTCTCCCCGCTCTGTAAAGTAGATAGAGTGGAT
TTTATGTCCCTTATTACCTTTCAGGATACTTTGACTCAGGGAGATAAAGTAACTTGGGTACAGCTACTC
AGCTGGTGAAGAACACAGGCAGAATGAGTGCCTGGGTCTTTTGACTTAAAATTCTGGATTTT

FLA311248 (S = G/C) (SEQ ID NO: 465)
CACTGTGCCTGGTGGCAGATCGGCATGAACTGGCCAGCTTCTGTGGCCCTGGAGGGCACAGGCAGAAAG
GCCACACTCAGTCCCATGATGAACTGTTTAAGACTTATTGTTGTCTCCCCGCTCTGTAAAGTAGATAGA
GTGGATTTTATGTCCCTTATTACCTTTCAGGATACTTTGACTCAGGGAGATAAAGTAACTTG
S
GTACAGCTACTCAGCTGGTGAAGAACACAGGCAGAATGAGTGCCTGGGTCTTTTGACTTAAAATTCTGG
ATTTTTCACAAAGATCCTCTTACTTTATTCATTTACATAATAAATATATTGAAGAGCTACTCTGTGC
CAAGCCCTGTGCCTAGATATACAGTGATAAATAAAGAGTAGCTTCTAGAGGTCACCTGGCGG

FLA311737 (Y = C/T) (SEQ ID NO: 466)
CCAAGTTCAGTGATAGAGAGCAGAGGTGAGGCGGCAGCAGAAACCACTTAAGGGACACCACGTGGCACT
CCTTCTGTGCTGAGAAGGCTGTCAGTAAGCTCACCATTTATTTCCTATTTTCTCTCCTGAGTTAAATAG
GAAACATGTCTCGCATTACTTGAAAAATCAAGTCAAACTATGCTCTTACTAGGAGTTATGGT
Y
CTTTTTATGTCTTAGATGATGCTTGATCTAGATGAATGCGGACTTGCTGTAGCTAGATAAATACAATGG
GAGTTTGAAGGTGTTTCGTAGCCCTGGAAATAGGTATTTCCTGTCAAAACAAGCTTTGTCATTGCCAGC
AGACAAAAGCATCAGTAACCTTGGTTGATAATCGTCATTTCTTAGGAATAAAGTAGACTGTA

FLA312038 (Y = C/T) (SEQ ID NO: 467)
AGGTATTTCCTGTCAAAACAAGCTTTGTCATTGCCAGCAGACAAAAGCATCAGTAACCTTGGTTGATAA
TCGTCATTTCTTAGGAATAAAGTAGACTGTAGAATTTTTTTTTAGCAGAAAGGAAACCCAAAGATAATTC
TAGTGCAAATCCCTCACTTTATAGAGCAGAAGCTCAAGTCCCAGAGGAACAAGTGGCTTGAA
Y
GAACATCAGAATTTTAGGGGCTGGATTTGTACCCTCCTGGTGCCAGCAGCCCACTTCCCTGCAGGAGGC
ACTCACCTTCCTTGCACAGGGGTATGAGTGTGGCCATTTTCCACCCATAATCTCTGTTAGCTCATGTTC
AATTGGGTTCCCATTGAAAGAAAAATGGACCAGTAAGTTGGAGCAGAATCATTCAGATGGTA

FLA312056 / SG13S30 (K = G/T) (SEQ ID NO: 468)
CAAGCTTTGTCATTGCCAGCAGACAAAAGCATCAGTAACCTTGGTTGATAATCGTCATTTCTTAGGAAT
AAAGTAGACTGTAGAATTTTTTTTTAGCAGAAAGGAAACCCAAAGATAATTCTAGTGCAAATCCCTCACT
TTATAGAGCAGAAGCTCAAGTCCCAGAGGAACAAGTGGCTTGAACGAACATCAGAATTTTAG
K
GGCTGGATTTGTACCCTCCTGGTGCCAGCAGCCCACTTCCCTGCAGGAGGCACTCACCTTCCTTGCACA
GGGGTATGAGTGTGGCCATTTTCCACCCATAATCTCTGTTAGCTCATGTTCAATTGGGTTCCCATTGAA
AGAAAAATGGACCAGTAAGTTGGAGCAGAATCATTCAGATGGTATAACATAAGGAAAAACTT

FLA314532 (Y = C/T) (SEQ ID NO: 469)
GTGAGGCAAAAGTACTTTGTCGGTTACCTAGGAGAGAGAACGCAGAGGTAGGTAACTGGGACTACTAAA
GAACTGTGGAGCGATTCCTGATTTTTGAGCAGGAAGAGTGACAATTCAAAACAGTATTTGACTAGATTC
ACGGCTCCGTAGCATCCCCTTGGGTGGGAGGGGGAAGGCTGACTAGGACCTCTGATTCTTCT
Y
TCCCTGAGCTTTGAAGGCTCTGAAAATACAGCTGGGGGGACTTGCCCAGTTTTCTTATTAAGCAATTCC
TCCGCATGGTGCTGGCTTTCAAAGGGTGCTTCAGTGCTGTTTGCTGCACGTGCCTTGCAGCCCCACACC
CTGCACTCCCGCCCTGCAGAGTCTGGCGCTGGAATGACATTTTAGGTCTGGGTTCCCAGGCC

FLA315014 (R = G/A) (SEQ ID NO: 470)
CATATCTTTCAGGGACCAGAAGAAAGAATGTTGGGAAAATAAGATGCAGTAAGATGCAGACATGACAGC
AGGGTGCAGCGGCTCACGCCTATAATCCCAGCACTTTGGGAGGCTGAGGTGGGTGGATCACCTGAGGTC
AGGAGTTTGAGACCAGCCTGGCCAACATGGTGAAACCCCGTCTCTACTAAAAAATATACAAA
R
CATTAGCCAGGCATGGTGGTGGGCGCCTGTAATCCCAGCTACTCCATAGGCTGAGGCTGGAGAATCGCT
TGAACCCAGGAGGCAGAGGTTGCAGTGAGCCGAGATTGCGCCACTGCACTCCAGCCTGGGCAACAAAAG
CAAAACTCCATCTCAAAAAAAAAAAAAAAAAAAAAAAAAAAAGATGCAGACACGAGACTGTGA

FLA315232 (W = T/A) (SEQ ID NO: 471)

FIG. 7 L

GGTGGGCGCCTGTAATCCCAGCTACTCCATAGGCTGAGGCTGGAGAATCGCTTGAACCCAGGAGGCAGA
GGTTGCAGTGAGCCGAGATTGCGCCACTGCACTCCAGCCTGGGCAACAAAAGCAAAACTCCATCTCAAA
AAAAAAAAAAAAAAAAAAAAAAAAGATGCAGACACGAGACTGTGAAACTGACTAGCATCACC
W
TTGCATTGTTTATAGATGTTGCCAGACAGAAAGCCCCAAAGCAGCACAGTACCTTCCTGACATCTGGAC
TAGGAAATCTAGATTTTAGTAAAATACATGCTAATACTTACAGAAGAAATGTCGGCGTTAGAGTATGCC
GTCAGTTCCTTAGAGATTGCAATTCCTAATGCACTAGTATGGTTTCAGGTGCCAGGAACACG

FLA315355 (R = G/A) (SEQ ID NO: 472)
AAACTCCATCTCAAAAAAAAAAAAAAAAAAAAAAAAAAAGATGCAGACACGAGACTGTGAAACTGACTA
GCATCACCATTGCATTGTTTATAGATGTTGCCAGACAGAAAGCCCCAAAGCAGCACAGTACCTTCCTGA
CATCTGGACTAGGAAATCTAGATTTTAGTAAAATACATGCTAATACTTACAGAAGAAATGTC
R
GCGTTAGAGTATGCCGTCAGTTCCTTAGAGATTGCAATTCCTAATGCACTAGTATGGTTTCAGGTGCCA
GGAACACGTTCTGTGAGGCTGCTGCCCCAGGTGCTGACCCCAGCCTTCCACACCATTTTCCTTCCTTGT
GTTCACAGCCGCTCTGTCTTTTACAATAGCACCCCTCTCTAGTGGCTAATGGGCTCTATGAT

FLA315611 (K = G/T) (SEQ ID NO: 473)
GGTTTCAGGTGCCAGGAACACGTTCTGTGAGGCTGCTGCCCCAGGTGCTGACCCCAGCCTTCCACACCA
TTTTCCTTCCTTGTGTTCACAGCCGCTCTGTCTTTTACAATAGCACCCCTCTCTAGTGGCTAATGGGCT
CTATGATTAGATAGCATCCTTCAGTAGTGATAAAGGCAGTGACATCCTAGGGAGGTCAGCGG
K
TGAAAGCGCTATATCTGGAAAACCTGAGAGCCTGTGAAGCTCAAGGACTTGACGGGGTTAGACCGTGAG
CCGGGCTGCAGCTGGAAAAAGAATGACTGTTCTTTCAGCAGATCCTTCCCTGTGCCATCTCTTTCTTCA
TTCCTCTCTAGTGGCATTCTTATTTATCCTCTAAAACCACAATTCCATTATCTCTCCTATTC

FLA316131 (S = G/C) (SEQ ID NO: 474)
AAGAGGGTCTTCTCTTTTGCCTGGCTCCCTATGCAGCCCTATCTTACCCCCTGCAAAGTCCCAGGGATG
TGGCTCAGTCACTGCTCCTCTCTTCATCTGTCACCACTTGCTTGAGATCCTACAGCTGCTTTAATTCCG
AGACCATCTGCAGAACATGACAAAATTTGTCCACCTACCCACATGTCCTTTTAACTTTAAAG
S
CTTTACTAACTGATTCCTATTAGGGAATGAACAGAGGTGGCAAAAATAAACAATAGGAGATTGATTTAC
AAGAAATCTTTAAAATAGTAGATTTCTTCGGACCTCATTGAAATATAAATGGCCTGCCTTCTTGTGTCC
CTCCCTGGTCTCCCTCTTTAGGTGATAAGAAGAAGATCCTGCCAGCCCCATAACCCGCCATC

FLA316408 (M = C/A) (SEQ ID NO: 475)
CTTTAAAATAGTAGATTTCTTCGGACCTCATTGAAATATAAATGGCCTGCCTTCTTGTGTCCCTCCCTG
GTCTCCCTCTTTAGGTGATAAGAAGAAGATCCTGCCAGCCCCATAACCCGCCATCTGCGCGGGTTCTAG
ACCCCCTTCTCCTCCCCTCTGGCCGTGGTAGGCATTACTGATGAATCATGGTGCTCTTTCTT
M
CAGAGACCAAACCTGGCCTCGGAATCCTTCTTAACACAGATACTGCTTAACACAACCACTCTGAGCAGC
TGTCATAAGTAGAAGTAATAGATACTAGAAGAAATGTCTAAGCCTAATCTAGACCAAAATACGGCCTGA
TATAGATGCAAGCCAGAGGGGCTTTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGTCT

FLA316472 (R = G/A) (SEQ ID NO: 476)
CCCTGGTCTCCCTCTTTAGGTGATAAGAAGAAGATCCTGCCAGCCCCATAACCCGCCATCTGCGCGGGT
TCTAGACCCCCTTCTCCTCCCCTCTGGCCGTGGTAGGCATTACTGATGAATCATGGTGCTCTTTCTTCC
AGAGACCAAACCTGGCCTCGGAATCCTTCTTAACACAGATACTGCTTAACACAACCACTCTG
R
GCAGCTGTCATAAGTAGAAGTAATAGATACTAGAAGAAATGTCTAAGCCTAATCTAGACCAAAATACGG
CCTGATATAGATGCAAGCCAGAGGGGCTTTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGTCTAG
AAGCTACTTGCTGAGATCTTCTTCAGTTGGGCCCATCTCCTCCCCAGGCCTCTCTTCTGTTC

FLA316515 (M = C/A) (SEQ ID NO: 477)
CCCCATAACCCGCCATCTGCGCGGGTTCTAGACCCCCTTCTCCTCCCCTCTGGCCGTGGTAGGCATTAC
TGATGAATCATGGTGCTCTTTCTTCCAGAGACCAAACCTGGCCTCGGAATCCTTCTTAACACAGATACT
GCTTAACACAACCACTCTGAGCAGCTGTCATAAGTAGAAGTAATAGATACTAGAAGAAATGT
M
TAAGCCTAATCTAGACCAAAATACGGCCTGATATAGATGCAAGCCAGAGGGGCTTTATGGTTAAATGCA
AGGAGATTTTCAACCCTGCCGTCTAGAAGCTACTTGCTGAGATCTTCTTCAGTTGGGCCCATCTCCTCC
CCAGGCCTCTCTTCTGTTCCTGGGCTATGTCACACTTGGACTCTGCAGACACCTAATGCTCT

FIG. 7 M

FLA316569 (K = G/T) (SEQ ID NO: 478)
CGTGGTAGGCATTACTGATGAATCATGGTGCTCTTTCTTCCAGAGACCAAACCTGGCCTCGGAATCCTT
CTTAACACAGATACTGCTTAACACAACCACTCTGAGCAGCTGTCATAAGTAGAAGTAATAGATACTAGA
AGAAATGTCTAAGCCTAATCTAGACCAAAATACGGCCTGATATAGATGCAAGCCAGAGGGGC
K
TTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGTCTAGAAGCTACTTGCTGAGATCTTCTTCAGTT
GGGCCCATCTCCTCCCCAGGCCTCTCTTCTGTTCCTGGGCTATGTCACACTTGGACTCTGCAGACACCT
AATGCTCTTGGGACCTGCTTTAGTTCTTGACCTCACCAACCGAGGAGGAATTGCTAGATGAG

FLA316607 (Y = C/T) (SEQ ID NO: 479)
TCCAGAGACCAAACCTGGCCTCGGAATCCTTCTTAACACAGATACTGCTTAACACAACCACTCTGAGCA
GCTGTCATAAGTAGAAGTAATAGATACTAGAAGAAATGTCTAAGCCTAATCTAGACCAAAATACGGCCT
GATATAGATGCAAGCCAGAGGGGCTTTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGT
Y
TAGAAGCTACTTGCTGAGATCTTCTTCAGTTGGGCCCATCTCCTCCCCAGGCCTCTCTTCTGTTCCTGG
GCTATGTCACACTTGGACTCTGCAGACACCTAATGCTCTTGGGACCTGCTTTAGTTCTTGACCTCACCA
ACCGAGGAGGAATTGCTAGATGAGATCCTTCCCCCGGAATTTCTCTCTTGAACCCCAGATGG

FLA316763 / SG13S32 (M = C/A) (SEQ ID NO: 480)
AGGGGCTTTATGGTTAAATGCAAGGAGATTTTCAACCCTGCCGTCTAGAAGCTACTTGCTGAGATCTTC
TTCAGTTGGGCCCATCTCCTCCCCAGGCCTCTCTTCTGTTCCTGGGCTATGTCACACTTGGACTCTGCA
GACACCTAATGCTCTTGGGACCTGCTTTAGTTCTTGACCTCACCAACCGAGGAGGAATTGCT
M
GATGAGATCCTTCCCCCGGAATTTCTCTCTTGAACCCCAGATGGTCCGTTGCCCCTTTCCAGAAGTTGC
TCCAGCCCTGTCCGCTTAGGAAGTTCAGTGTCATCCTTGATCCAGTGGGTAGGGAAGACATTCCATAAT
GAATGCCCCAGTCTGAGCTTCTTCCTTCAGGCTTCAGGCTGCCCTGCGAGGATTTTGCAGCT

FLA317496 (R = G/A) (SEQ ID NO: 481)
GAGTAGCTGAGACTACAGGTGTGCACTACCACACCCAGCTAATTTTTTGTATTTTTAGTAGAGATAGGG
TTTAGCTATGTTGGCCAGGCTGGTCTCGAACTGCTGAACTCAAGCAATCTGCCATCCCCGGCCTCCCAA
AGTACTGGGAGTATAGGCATAAGCCACCCATGATGCCCAGCCTGAATCTTGGTTTCTTCCCC
R
TTCATTTAAGCTATTACCTGGGCCTGAACTCAATGGCACCTGGCACCAACTGGCAACTGACTCTTGGTC
TTTTATTACCTACCTTCCCTAGCAGGCACTGGGTTGCTCCCTCTTCCTATCCCATGGAGTCCTGTCCTC
TGTTGGGGCTCCTACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAATGGTGGGTGGGCA

FLA317619 (R = G/A) (SEQ ID NO: 482)
TCCCCGGCCTCCCAAAGTACTGGGAGTATAGGCATAAGCCACCCATGATGCCCAGCCTGAATCTTGGTT
TCTTCCCCATTCATTTAAGCTATTACCTGGGCCTGAACTCAATGGCACCTGGCACCAACTGGCAACTGA
CTCTTGGTCTTTTATTACCTACCTTCCCTAGCAGGCACTGGGTTGCTCCCTCTTCCTATCCC
R
TGGAGTCCTGTCCTCTGTTGGGGCTCCTACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAATGGTG
GGTGGGCAATGACTGCCAACTCTTGAGGCCAATGAACTCAGGTTACCCCACTCCTCCTCCTCCTGAGTT
GCTCACTCACTCCTCATTCACTCAACATTGATTCAGTAGATATTTGCTACCTGCTCTGTGCC

FLA317620 (Y = C/T) (SEQ ID NO: 483)
CCCCGGCCTCCCAAAGTACTGGGAGTATAGGCATAAGCCACCCATGATGCCCAGCCTGAATCTTGGTTT
CTTCCCCATTCATTTAAGCTATTACCTGGGCCTGAACTCAATGGCACCTGGCACCAACTGGCAACTGAC
TCTTGGTCTTTTATTACCTACCTTCCCTAGCAGGCACTGGGTTGCTCCCTCTTCCTATCCCA
Y
GGAGTCCTGTCCTCTGTTGGGGCTCCTACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAATGGTGG
GTGGGCAATGACTGCCAACTCTTGAGGCCAATGAACTCAGGTTACCCCACTCCTCCTCCTCCTGAGTTG
CTCACTCACTCCTCATTCACTCAACATTGATTCAGTAGATATTTGCTACCTGCTCTGTGCCA

FLA317647 (Y = C/T) (SEQ ID NO: 484)
TAGGCATAAGCCACCCATGATGCCCAGCCTGAATCTTGGTTTCTTCCCCATTCATTTAAGCTATTACCT
GGGCCTGAACTCAATGGCACCTGGCACCAACTGGCAACTGACTCTTGGTCTTTTATTACCTACCTTCCC
TAGCAGGCACTGGGTTGCTCCCTCTTCCTATCCCATGGAGTCCTGTCCTCTGTTGGGGCTCC
Y

FIG. 7 N

ACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAATGGTGGGTGGGCAATGACTGCCAACTCTTGAGG
CCAATGAACTCAGGTTACCCCACTCCTCCTCCTCCTGAGTTGCTCACTCACTCCTCATTCACTCAACAT
TGATTCAGTAGATATTTGCTACCTGCTCTGTGCCAGGTACCAGGTCAGTTGCTGAAGGAGTA

FLA317733 (W = T/A) (SEQ ID NO: 485)
CACCTGGCACCAACTGGCAACTGACTCTTGGTCTTTTATTACCTACCTTCCCTAGCAGGCACTGGGTTG
CTCCCTCTTCCTATCCCATGGAGTCCTGTCCTCTGTTGGGGCTCCTACTGATCCTCTTGGCAATATGAA
GTTCTCAGCTCAATGGTGGGTGGGCAATGACTGCCAACTCTTGAGGCCAATGAACTCAGGTT
W
CCCCACTCCTCCTCCTCCTGAGTTGCTCACTCACTCCTCATTCACTCAACATTGATTCAGTAGATATTT
GCTACCTGCTCTGTGCCAGGTACCAGGTCAGTTGCTGAAGGAGTAACAGTGAACATGACGGAGTCTTTG
TCCCCAAGGAGACCCAAGGTGTCTCCTAGAGCCAGGGGCACATTGCAAGACCAAATATATTC

FLA317744 (Y = C/T) (SEQ ID NO: 486)
AACTGGCAACTGACTCTTGGTCTTTTATTACCTACCTTCCCTAGCAGGCACTGGGTTGCTCCCTCTTCC
TATCCCATGGAGTCCTGTCCTCTGTTGGGGCTCCTACTGATCCTCTTGGCAATATGAAGTTCTCAGCTC
AATGGTGGGTGGGCAATGACTGCCAACTCTTGAGGCCAATGAACTCAGGTTACCCCACTCCT
Y
CTCCTCCTGAGTTGCTCACTCACTCCTCATTCACTCAACATTGATTCAGTAGATATTTGCTACCTGCTC
TGTGCCAGGTACCAGGTCAGTTGCTGAAGGAGTAACAGTGAACATGACGGAGTCTTTGTCCCCAAGGAG
ACCCAAGGTGTCTCCTAGAGCCAGGGGCACATTGCAAGACCAAATATATTCAACTTACCAAA

FLA317815 (R = G/A) (SEQ ID NO: 487)
TCCCATGGAGTCCTGTCCTCTGTTGGGGCTCCTACTGATCCTCTTGGCAATATGAAGTTCTCAGCTCAA
TGGTGGGTGGGCAATGACTGCCAACTCTTGAGGCCAATGAACTCAGGTTACCCCACTCCTCCTCCTCCT
GAGTTGCTCACTCACTCCTCATTCACTCAACATTGATTCAGTAGATATTTGCTACCTGCTCT
R
TGCCAGGTACCAGGTCAGTTGCTGAAGGAGTAACAGTGAACATGACGGAGTCTTTGTCCCCAAGGAGAC
CCAAGGTGTCTCCTAGAGCCAGGGGCACATTGCAAGACCAAATATATTCAACTTACCAAAATAATCATA
GACCTAGTTCTCAAAAAGCAAGAAGACTGATTCCTCGTTGTCATTTCTCCTCCTCAGCATCA

FLA318219 (W = T/A) (SEQ ID NO: 488)
TTTTAGAGTCTGTGGGCCCCTCCAAGTGTGGAGTATGGTGTTACTTCACCAGAGTTTGAGGAGAAACAT
TCTTCTTTTGGAAGGCCGGGGAGCATAGATGGATATCAAGGCTGCTGTTTCTAAAAGCGAAACCCACCA
AACAACAGTATTAGAATCATCTGTGGTGCTTATTAAAGATACAGATTCCTGGGCCCCATCCC
W
GACTTATGAATCAGAATCTCTGCCAGAGGAAGCCTGAGAATTTGCATTCTCAGATGATTCTGCATTCTC
AGATAACACATTCTTTAGGTGATTCTTACACACACTGGAGTTTGGGAATCGCTGAAGGCTGTTCACTTC
TCTTTTCTGAGAAATGATTCATTCATTTCAGAAATATTTGCAGAGGTCCTTATTTATTGGAG

FLA319969 (K = G/T) (SEQ ID NO: 489)
GGTGGCCTCATTCGTGTGATAAATCTGAGCCACCACGATATTTGACTTTTCACAATTTAATTTATCTGA
ACCCTCTATTCTCTGGCTAAAAAATATCCCTTACTTGGACTTCTTTATTTTATTTTCAATTCCCTTACC
AGCACTAGCAGGGGACTCTGTACTCATCTGCTGGCGCTGCCATAACAAAGCACTGCAGCCTG
K
GGGGCTCAAACCACAGAATTTATTCTCTCACAGTCCTAGAGGCTAGAAGTCCAAGATCAAAGTGTGGGC
AGGGTCGGTTTCTCCTGCAGCCTCTCTCCTTGGCTTATAGAGTGCCACCTTCTACCTGTGTCTTCACAT
CATCACCTCACTGAGCATGTCTGTGTCCAAATCTCCCCTTCTTATAAGACCCCAGTCATACT

FLA320261 (R = G/A) (SEQ ID NO: 490)
TCTCTCCTTGGCTTATAGAGTGCCACCTTCTACCTGTGTCTTCACATCATCACCTCACTGAGCATGTCT
GTGTCCAAATCTCCCCTTCTTATAAGACCCCAGTCATACTGGATGAGGATCCACCCATATGAGTTCATT
TTACCTTAATTATCTCTTTAAACACCCTGTCTCCAAATACAGTCCCATTCTGAGGAACTGAG
R
GTAAAGATTCAACATATGAATTTTGGAAGGGACCTAATTCAGCCCACAACACCCTCTTTTGGGATGTTT
ATTTTCCCCCTTAAGGAGCTAGTTAGGATGTCTTATCTCATGAACATGACTGTGAACAGGAAAACAGGG
AGAGAATGAAGCTGGCCAAGGAACAGGGCTGGTGTCAGCTAGCAGTGCTTTTCTGATGTGAG

FLA320393 / SG13S42 (R = G/A) (SEQ ID NO: 491)

FIG. 70

TTCATTTTACCTTAATTATCTCTTTAAACACCCTGTCTCCAAATACAGTCCCATTCTGAGGAACTGAGA
GTAAAGATTCAACATATGAATTTTGGAAGGGACCTAATTCAGCCCACAACACCCTCTTTTGGGATGTTT
ATTTTCCCCCTTAAGGAGCTAGTTAGGATGTCTTATCTCATGAACATGACTGTGAACAGGAA
R
ACAGGGAGAGAATGAAGCTGGCCAAGGAACAGGGCTGGTGTCAGCTAGCAGTGCTTTTCTGATGTGAGT
GGGTCCCACAGGGAGCTTGTTAAAATGCAGATTCTGATTCATTAGGTTCCAGAGGGACCTGAGATTTCC
CATTTCTGACAAGTTTCCAGTGTGGGGGCTGATGCTGCTGGTCCACGGACCATACTTTGAGT

FLA320595 (K = G/T) (SEQ ID NO: 492)
CAGGGAGAGAATGAAGCTGGCCAAGGAACAGGGCTGGTGTCAGCTAGCAGTGCTTTTCTGATGTGAGTG
GGTCCCACAGGGAGCTTGTTAAAATGCAGATTCTGATTCATTAGGTTCCAGAGGGACCTGAGATTTCCC
ATTTCTGACAAGTTTCCAGTGTGGGGGCTGATGCTGCTGGTCCACGGACCATACTTTGAGTA
K
CAAGGAGCTTGATACATAATGGCTGAGTGACTTTCAGACTCCTGCTGTAGAAAAATTATGAGTTGGCTG
GGCGTGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGTGGGCAGATCACCTGAGGTCAG
GAGTTCGAGACCAGCCTGGCCAACATGGTGAAACACCATCTCTACCAAAAATACAAAAATTA

FLA321774 (Y = C/T) (SEQ ID NO: 493)
TCACTTAAGCCCAGAAGACTGAGGTTGCAGTGAGCCGAGATTGCACCACTGCACTCCAGCTTGGGCTAC
AGAGTGAGACTCTATCTCAAAAACAAAGAAACAAACAACAACAATAACAACAAAAACCAAGTCTCTCCC
TCCACTCAAAAATGCAAGGGCCTGTCTCCCATTGCTGGGTGCCCAGGTCTCATGAATGTAGA
Y
ATGAATTATTCCAGTCAGCCTCAGGAGAATAGAATGAGCCCTCAGATGCCGAAGCACCTTTCAGATTCC
ACCGGTTTTATCGGCTCATTTAAACTTCACTTCTAACACAGTCCTGCATTACACACGTGTCTGTCGTTA
TGGGCAGCTGCAGAGAGGGTCTTAATGGTCCTAATGCTCAGTGAGGATGCCCAATGGTCAAC

FLA321966 (R = G/A) (SEQ ID NO: 494)
AATGTAGATATGAATTATTCCAGTCAGCCTCAGGAGAATAGAATGAGCCCTCAGATGCCGAAGCACCTT
TCAGATTCCACCGGTTTTATCGGCTCATTTAAACTTCACTTCTAACACAGTCCTGCATTACACACGTGT
CTGTCGTTATGGGCAGCTGCAGAGAGGGTCTTAATGGTCCTAATGCTCAGTGAGGATGCCCA
R
TGGTCAACAGAACCTGCCATCTTCAGGCCATCAAGGAGCTCTGGAGTTAAGGAAATCATGAGAGCACAG
AGGGGCGGGTACAGCAGAGCCCTCGTGGTAATGGGTTTTGAGGTCTAGGCTCTCTTCACTTGGGTTTGA
AATAAGTTCAATGACTAGTAATAGCTGAGACACTTCTACCCTTCAAATGAAGTAAATGGGAA

FLA322025 (W = T/A) (SEQ ID NO: 495)
GAAGCACCTTTCAGATTCCACCGGTTTTATCGGCTCATTTAAACTTCACTTCTAACACAGTCCTGCATT
ACACACGTGTCTGTCGTTATGGGCAGCTGCAGAGAGGGTCTTAATGGTCCTAATGCTCAGTGAGGATGC
CCAATGGTCAACAGAACCTGCCATCTTCAGGCCATCAAGGAGCTCTGGAGTTAAGGAAATCA
W
GAGAGCACAGAGGGGCGGGTACAGCAGAGCCCTCGTGGTAATGGGTTTTGAGGTCTAGGCTCTCTTCAC
TTGGGTTTGAAATAAGTTCAATGACTAGTAATAGCTGAGACACTTCTACCCTTCAAATGAAGTAAATGG
GAAAATGGAGCATTGTTGAGTCCAGGGAGCTATAATTTAAACCCCATATATCTAAAAGGGGT

FLA322093 (R = G/A) (SEQ ID NO: 496)
TACACACGTGTCTGTCGTTATGGGCAGCTGCAGAGAGGGTCTTAATGGTCCTAATGCTCAGTGAGGATG
CCCAATGGTCAACAGAACCTGCCATCTTCAGGCCATCAAGGAGCTCTGGAGTTAAGGAAATCATGAGAG
CACAGAGGGGCGGGTACAGCAGAGCCCTCGTGGTAATGGGTTTTGAGGTCTAGGCTCTCTTC
R
CTTGGGTTTGAAATAAGTTCAATGACTAGTAATAGCTGAGACACTTCTACCCTTCAAATGAAGTAAATG
GGAAAATGGAGCATTGTTGAGTCCAGGGAGCTATAATTTAAACCCCATATATCTAAAAGGGGTAACATT
TTTGTGTGTGTGAAATTGGTGTCATTCGCACTGCATCTACAGTTTTCTTTTTCCTTCTCTTC

FLA323013 (R = G/A) (SEQ ID NO: 497)
ATTTATCTCTATACCCACAAACGACTAGTTTGTTTTCCTCAAACTAAATGATAATATTAAAAATACACA
TCCTGGCCAGGTGTGGTGGCTCATACCTGTAATCCCAGCACTTTGGGAGGCCGAGGCAGGTGGATCACT
TGAGGTCAGGAATTAAGACCAGCCTGGCCAATATGGTGAAAGCCTGTCTGTACTAAAAATAC
R
AAAATTAGCCAGGTATGCTGGTGGATGCTTATAATCCCAGCTACTTGGGAGGTTGAGGCAGGAGAATTG
CTTGAACCCGGGAGGTAGAGGTTGCAGTGAGCCAAGATCATGCCACTGCACTCCAGCTTGGGCAACAGA
GTGAGACTCCATCTCAAATTAAAAAAAATACACATCTGGCTTCTGGAAAAATTACTTGAAGA

FIG. 7P

FLA323316 / SG13S34 (K = G/T) (SEQ ID NO: 498)
AAGATCATGCCACTGCACTCCAGCTTGGGCAACAGAGTGAGACTCCATCTCAAATTAAAAAAAATACAC
ATCTGGCTTCTGGAAAAATTACTTGAAGATCTTTTATGACATCCATCCCTCTTCACACAGCCATGTGAA
TTAGGTTGGTATCTTCATATACTAGCATCGTGCCCAGCACTTCCATGTTATACAGTTTAAAA
K
GTTCTGTAATTCCCTGTGGGAACCTAAGATAATGCGAGGACCGTCATACGTGCCCCCAAATATTGGCAA
ACCAATGAATAAATGAATGAATGAGTTTATGAATCGCTAACTGGCTGTATTTAATGAAGTATGTGTGTT
GAGCCATTTCCCACAGTGTGGACAGATTTGTCCCACAATATGGGCCTCTTCCCAAAGGCCCT

FLA323366 (R = G/A) (SEQ ID NO: 499)
CAAATTAAAAAAAATACACATCTGGCTTCTGGAAAAATTACTTGAAGATCTTTTATGACATCCATCCCT
CTTCACACAGCCATGTGAATTAGGTTGGTATCTTCATATACTAGCATCGTGCCCAGCACTTCCATGTTA
TACAGTTTAAAATGTTCTGTAATTCCCTGTGGGAACCTAAGATAATGCGAGGACCGTCATAC
R
TGCCCCCAAATATTGGCAAACCAATGAATAAATGAATGAATGAGTTTATGAATCGCTAACTGGCTGTAT
TTAATGAAGTATGTGTGTTGAGCCATTTCCCACAGTGTGGACAGATTTGTCCCACAATATGGGCCTCTT
CCCAAAGGCCCTACCACCTAATGCCATCACACTGGGGATTTGATTTCAACATGTGAATTTGG

FLA324591 (R = G/A) (SEQ ID NO: 500)
GTGATACTTTATTATGTGTGTGGATTGTGTAATGATGAAGTCAGGGCATTTAGGGTCTTCATCACCTTG
ATTATCATTTCTATGTGTTGAGAACATTTCAAGTTCTCAGTTCCAGCTATTTTGAAATAGACAGTCCAT
TTTGTTAGCTACAGTCACCCAACCCGGCTGTCAGACATTGGAACTTACTCCTATTGAACTGT
R
TATTTGTACCCATTCACCAAACTCTCTTTGGGCTTTCAGTTTTACAACTGGGATGATCCTGGGAAAACT
AAAGTAAATCAGACACCCGACGTGTGAGCTAGGTTATAATATGCCCAGTGGACCCTGGGGACATCTTAG
CTTTCAGAGGTCATGCTGTCCAAGCTGACTGTGGGGCTTCCAGAAGGTGGGGAGAGGAAATG

FLA324601 (Y = C/T) (SEQ ID NO: 501)
ATTATGTGTGTGGATTGTGTAATGATGAAGTCAGGGCATTTAGGGTCTTCATCACCTTGATTATCATTT
CTATGTGTTGAGAACATTTCAAGTTCTCAGTTCCAGCTATTTTGAAATAGACAGTCCATTTTGTTAGCT
ACAGTCACCCAACCCGGCTGTCAGACATTGGAACTTACTCCTATTGAACTGTGTATTTGTAC
Y
CATTCACCAAACTCTCTTTGGGCTTTCAGTTTTACAACTGGGATGATCCTGGGAAAACTAAAGTAAATC
AGACACCCGACGTGTGAGCTAGGTTATAATATGCCCAGTGGACCCTGGGGACATCTTAGCTTTCAGAGG
TCATGCTGTCCAAGCTGACTGTGGGGCTTCCAGAAGGTGGGGAGAGGAAATGATGCAATGGC

FLA324849 (S = G/C) (SEQ ID NO: 502)
CCTGGGAAAACTAAAGTAAATCAGACACCCGACGTGTGAGCTAGGTTATAATATGCCCAGTGGACCCTG
GGGACATCTTAGCTTTCAGAGGTCATGCTGTCCAAGCTGACTGTGGGGCTTCCAGAAGGTGGGGAGAGG
AAATGATGCAATGGCCCATCAGAGGCACTACTTGGGGCCTGGGGCCAGAGTGCATGTCTAAG
S
CATTAAGGGGAGGGGAGAGCAGCCTTCATAATTATGAAGAGGAGTCTCAGGTGCACAGCTTCTGATGAG
GGACAGCTTCTAATTGAAGACAGCATTGTGTAATGCTCAAACTCCCTGTCTTCAGAGTGCCTGCTGTAT
CCCACCATCAGTTCTGTGACTTCTCCCTAAGCCTCAATTTTGCATGTGTTACATTGGGATAA

FLA325369 (Y = C/T) (SEQ ID NO: 503)
TTCCTGCATAGCAAATTCTTGCAAATGTAGGGACTCAAAACAATATAAATTTATTATCTGACAGTTTTT
CTGGGTCAGAGGTCTTACTAGGCTGTAATCAGAGGGCAACCAAAGCTGTGATCTCAGCTGAAGCTCAGG
ATTCTCTTCCAAGCTCACTGGTTGTTGGCAGAATTCAGTTCTTTCCAGTTGGAAGACTAAAG
Y
CTACAGTCTTCAGTCTCTAGAAGCCTTTTCTCTGGCACAGGTTTCTCTACAACATGGCCATTTATGTCT
TTAAGGCCAATAGGAGAACATGATTAGCATATTTTTTTTAAGTGAACTTTAGACCCTTTTTTAAAGGCC
TATCTGATTAGGCCAGGCCCAAGTGAGCTTTAAGTCAACTGATTAGAGATCTTAATTACATC

FLA326187 (R = G/A) (SEQ ID NO: 504)
CTGGGATTACAGACACACACTGCCACGCCTGGCTAATTTTTGTATTTTTAGTAGAGACGAGGTTTTGCC
ATGTTGGCCAGGCTGGTCTTGAACTCCTGACCTCAAGTGATCCGCCCACCTCAGCCTCCCAAAGTGCTG
GGATTACAGACGTGAGCCACCATTAACCATTTTTCTATCTCCTGTGGGAAAGGGCACAGTGA
R

FIG. 7Q

AGAACAGATGAAGCTGAGACATACAAGTGAACTCCTCCCTCCTCTCCATTTAGACTAAAATAGGATTAT
TCATACTGAGATTCTCCCTGGTTGCAAAGAGATAATCTGTGCAACTGGGTTTTTACAATTATCCCTACC
CTATGCTTTCCTCATCTGTCTTCCTCGTAGTCAGCTCAGGCTGCTATAACAAAACACCATAA

FLA326657 (R = G/A) (SEQ ID NO: 505)
CTGGCAGATTCGGTGTCTAATGAGGTCCTGCTTTCCAGTTTATAGACAGTGCCTTATCGCTACCGCCTT
ACACAGTGGAAGGAGAGGACGAGAAGCTCCTTGGGCTTTTTTTTGTTTCTTTCTTTCTCTCTCTCTCTC
TTTTTTTTTTTTTTTAATAAGGTCACTATCTTAGTCCATTTTGTGTTGCTAAAAGGAACATCT
R
AGGTTGAGTAATTTATTTTATTTTAAAAAGTGGCCAGGCATGGAGGCTTATCCTGTAACCCTAATCCTT
TAGGAGGCCAAAACAGCAGGATTGTTTGAGGCCAGGAGTTCAAGACCAGCCTAGGCAAGATAGTGAGAC
CCCATCTACCCCATCTCTACTAAAATTTTAAAAAATTAGCTGTGTGTTGTAAAGTGTGCTTG

FLA327265 (Y = C/T) (SEQ ID NO: 506)
TCATGGGGGAAGACGAAGGAGAGCTGGCACGTGCAGATATCACGTGTTGAGGGCAGAAGCGAGAGAGAG
AGGGGAGAGATGCCAGGCTCTTTTTAACAACCAGCACTGGGGAAACTAATAGAGTGAGAGCTCACTGAC
TCCTGAGGGAGGACATTAATCTATTGATGAGCGACCTGCCTCCATGACCCAAACACCTCCAA
Y
GATACCCCACCTCCAACACTGCCACACTAGGGATTAACTTTCAACTTGAGATTTAGAGGGGGGAAACTT
ACAAACTATCGCAGGCACTAATACCACTCATGAGGGCTCCACCTTCATGACCTAATCACTTCCTAAAGG
CCTTACCTCTTAATCTCATCACATTGAGGATTCGATTTCAACTTGAATTTTGGGGGGACACC

FLA328964 (Y = C/T) (SEQ ID NO: 507)
AACCTGTCTTAAAACATGAAAGTTCCTTAGTGCTACCCCCAGAGGTATGATTTGGTAGGTCAAGGATAG
GGCCTGGAAATTCACATTCTTGTTAAGATGTTCTTCATCCGGGGTTTGTTGACCACCTTTTCAGAAGAT
TTTTGCTCTGTAGCTGTACTACCCAATGCAGTAGTTCGTAGTCAGTGTGGCTCCTGAGCCCT
Y
GAAGTGTAGCTCCTCTGAACTGAGACGTGCTGTAAATGTAAATTGCACACCGGAGTTTGAAGAGTTAAT
ACAAAGAAAAAGGAATGCAAAACATCTCATTAATAATGCTTTACACTGATTACATATTGAAATGGTAAT
CTTGTAGATATAGTGCGTTAAATAAAATATACTGTTAGGCTTAATTTCACGTCTTTATACTT

FLA330265 (Y = C/T) (SEQ ID NO: 508)
ATTCAGCCAATCAACAAGAGGGCAAAAGAACAAACATTTGATGTGTAATTACTTAATTTAGTGCATATG
CATTTGGGTCCTCAATGTCAGCACTATGGCAACCAGAACATGGCCACAATAACTGTCTGGAAATGTCTA
TTCTTACCTGGACCCAGCAGGCCATGCCCCACTGATTATATAATCTCCCTCTCTCCTTGTTA
Y
GGTCTGAATGCTTGCATCCCTCAAAAATTCATGTGTTGAAATCCTAACCCCCAAGGTGATGATATTAGG
AGGTCGGCCTTTTGAGAGGTAATTAGGTCATGAAGACAGCATCCTCATGAATGGGATTAGTGTCCTTAT
AAAATAGGCCCAAGGGAGCTCATTCACTTTGTCCACCATGTGAGAACACAGCGAGAGGGCAC

FLA330455 (Y = C/T) (SEQ ID NO: 509)
CTCCTTGTTACGGTCTGAATGCTTGCATCCCTCAAAAATTCATGTGTTGAAATCCTAACCCCCAAGGTG
ATGATATTAGGAGGTCGGCCTTTTGAGAGGTAATTAGGTCATGAAGACAGCATCCTCATGAATGGGATT
AGTGTCCTTATAAAATAGGCCCAAGGGAGCTCATTCACTTTGTCCACCATGTGAGAACACAG
Y
GAGAGGGCACCATTTATGCACCAGGAAATGGGCCTTTTCCAGACAATCTGTCGGTGCCTGGATCTTGGA
CTTCACAGCCTCTAGAACTGTGAGAAATTAATTTGTTTTTTATAAGCCACCAAATCTATGGTTTTTTTT
ATAGAAACCGTAATGGACTAAAACACTCCCTAATTATATTTAAACTTATCAGTGCACTGGGC

FLA331234 (R = G/A) (SEQ ID NO: 510)
GACAGGTAGGCAAAGGAGGTGGGTTGCAGGGGAGTTGAGGGTTGCCTGTGTACTTTTCTAGACTGTTCC
ACTTCACATCAGTGAAATATTCCCAATTGATACTATCATGAAACAAAGCAAATGAAATGCTGAGCACGG
AGCTTCGTCTTGATGAAATGCTGAAAGAAAAGAAAGGAAAAATAAAGTAGCCATTATTTTTG
R
CCCTTCCTCCCACCCCCATGTTTACTACTCTTATTTCTCTTTTGTATTGTTGTGTTGGAAGCACAGCAT
CAGAAAAACTCCCAGTTTTGAGAGATAACTCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGG
ATGCCACCGTGAGGTCCAGGACGTAAAGAGGAAAAAAACAGACAAAAAAATCCATATGAAAT

FLA331374 (Y = C/T) (SEQ ID NO: 511)

FIG. 7R

GCTTCGTCTTGATGAAATGCTGAAAGAAAAGAAAGGAAAAATAAAGTAGCCATTATTTTTGCCCTTCCT
CCCACCCCCATGTTTACTACTCTTATTTCTCTTTTGTATTGTTGTGTTGGAAGCACAGCATCAGAAAAA
CTCCCAGTTTTGAGAGATAACTCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGGA
Y
GCCACCGTGAGGTCCAGGACGTAAAGAGGAAAAAAACAGACAAAAAAATCCATATGAAATGAAAATGTG
AAAGAGGCGCTTTCGAGCAGATGAGTGTTGTAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGC
TTGCTGCACCTGGCGGGATAAACACTGGTCTAACAGAGGATCCTTGTTTCAAGGAGGCTGCC

FLA331395 (R = G/A) (SEQ ID NO: 512)
GAAAGAAAAGAAAGGAAAAATAAAGTAGCCATTATTTTTGCCCTTCCTCCCACCCCCATGTTTACTACT
CTTATTTCTCTTTTGTATTGTTGTGTTGGAAGCACAGCATCAGAAAAACTCCCAGTTTTGAGAGATAAC
TCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGGATGCCACCGTGAGGTCCAGGAC
R
TAAAGAGGAAAAAAACAGACAAAAAAATCCATATGAAATGAAAATGTGAAAGAGGCGCTTTCGAGCAGA
TGAGTGTTGTAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCTTGCTGCACCTGGCGGGATAA
ACACTGGTCTAACAGAGGATCCTTGTTTCAAGGAGGCTGCCTTTTATTTGGGGGGACAAAAT

FLA331473 (R = G/A) (SEQ ID NO: 513)
CTTTTGTATTGTTGTGTTGGAAGCACAGCATCAGAAAAACTCCCAGTTTTGAGAGATAACTCAGTGTTT
AGTTCACTTAAACCTGAGAAAGGAGAAGAGGATGCCACCGTGAGGTCCAGGACGTAAAGAGGAAAAAAA
CAGACAAAAAAATCCATATGAAATGAAAATGTGAAAGAGGCGCTTTCGAGCAGATGAGTGTT
R
TAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCTTGCTGCACCTGGCGGGATAAACACTGGTC
TAACAGAGGATCCTTGTTTCAAGGAGGCTGCCTTTTATTTGGGGGGACAAAATTGTTCTTGAAAGCTGC
TCAGTGGTTCAAGCTACAGCATGGTGGACTAGCAGAATGGACTCCAGGGCCTCCGAGGAGAC

FLA331517 (Y = C/T) (SEQ ID NO: 514)
AGTTTTGAGAGATAACTCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGGATGCCACCGTGAG
GTCCAGGACGTAAAGAGGAAAAAAACAGACAAAAAAATCCATATGAAATGAAAATGTGAAAGAGGCGCT
TTCGAGCAGATGAGTGTTGTAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCTTGC
Y
GCACCTGGCGGGATAAACACTGGTCTAACAGAGGATCCTTGTTTCAAGGAGGCTGCCTTTTATTTGGGG
GGACAAAATTGTTCTTGAAAGCTGCTCAGTGGTTCAAGCTACAGCATGGTGGACTAGCAGAATGGACTC
CAGGGCCTCCGAGGAGACAGTGACTGCTGCCAGAAATAGTCAAGGATAGAAAGGAAGGACTT

FLA331526 (Y = C/T) (SEQ ID NO: 515)
AGATAACTCAGTGTTTAGTTCACTTAAACCTGAGAAAGGAGAAGAGGATGCCACCGTGAGGTCCAGGAC
GTAAAGAGGAAAAAAACAGACAAAAAAATCCATATGAAATGAAAATGTGAAAGAGGCGCTTTCGAGCAG
ATGAGTGTTGTAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCTTGCTGCACCTGG
Y
GGGATAAACACTGGTCTAACAGAGGATCCTTGTTTCAAGGAGGCTGCCTTTTATTTGGGGGGACAAAAT
TGTTCTTGAAAGCTGCTCAGTGGTTCAAGCTACAGCATGGTGGACTAGCAGAATGGACTCCAGGGCCTC
CGAGGAGACAGTGACTGCTGCCAGAAATAGTCAAGGATAGAAAGGAAGGACTTCACTGAGGC

FLA331651 (S = G/C) (SEQ ID NO: 516)
CGCTTTCGAGCAGATGAGTGTTGTAGATTACAGTGTTGAGAGCTGTTTGTGTCCAGAGCTGCTTGCTGC
ACCTGGCGGGATAAACACTGGTCTAACAGAGGATCCTTGTTTCAAGGAGGCTGCCTTTTATTTGGGGGG
ACAAAATTGTTCTTGAAAGCTGCTCAGTGGTTCAAGCTACAGCATGGTGGACTAGCAGAATG
S
ACTCCAGGGCCTCCGAGGAGACAGTGACTGCTGCCAGAAATAGTCAAGGATAGAAAGGAAGGACTTCAC
TGAGGCCTGGGAGAAGATTATGGAATGGGACTGACAGCAGTGACGGGGAGTAAAAGGGGGTGTCTGGGG
GAATTGTGCCCCATGGTGAGAGCTAGAGGGTTCACAAAGACTTAACCCGACGCATCTCTCTC

FLA331841 (R = G/A) (SEQ ID NO: 517)
TAGCAGAATGGACTCCAGGGCCTCCGAGGAGACAGTGACTGCTGCCAGAAATAGTCAAGGATAGAAAGG
AAGGACTTCACTGAGGCCTGGGAGAAGATTATGGAATGGGACTGACAGCAGTGACGGGGAGTAAAAGGG
GGTGTCTGGGGGAATTGTGCCCCATGGTGAGAGCTAGAGGGTTCACAAAGACTTAACCCGAC
R
CATCTCTCTCACCCTGGAGATTGGGCCCGTTCAATCTAACTGGATGGCTATAATTTAAAAGGTTTAGGT
ATTATGACAAACATGGATATATTAGGTGATAGCAATGCAAAATGCATATGGCTTCTTGATATAAAACAC
AAGACTTGAAAGCAGCATCTTTGGCTGGGTACTACAGCCACCCTCCTCTGTCACTAAGGGAG

FIG. 7 S

SG13S86 (R= G/A) (SEQ ID NO: 518)
CAGCAACATATCTGTGTGCCTGTCTGGGTTGTAAAAAGGGTCAAAGATCAATGCAGCAGGCAGCTACAT
GCTGGCAAAAGCCAGAGGCAGCTGGTCTGTTTGCCTGTGCCAGGAAACCACTGGGAATGGGGTTGTGTG
TTATTCTAGGAGAAAGTCGTCCCAGCAGCAGCTTCTCCAGGGGCATCCAAGAGCACTGAAAA
R
GGTTGCAAGATGACCCATGAGGCTGCAGGAAGAAAAGAACATGCATTTAATCTTGCTATCTGAAAAGTA
AGACATGAAGCTTTCCTCATTTTTAATATACACATGGACAGTAGTATGTGTATATAGTTTATATGCAAA
TATACTTGTTATAAGGTTGCATGCTCAAAATTTTTGGTTCATGGGGTGTGGGATCATAAATG

SNP13B_R1028729 (Y=C/T) (SEQ ID NO: 519)
CTACAAAAATTACCATCATATGCTGTCATGCATGTCTGCCAGTCTATTTATCATATTATTTAAGAAACA
AACATTTATTGAAGATTTATCATGTGCTCAGCACTGCCAAAGAGGAAATAAAGAGCATAATATCTATTC
TTAGAAAATAACATTAACACAAATAGAAAACAAGAAACCATAATGTTAAAAATATTACATAG
Y
AACACAGAAAGACAATGTATAATTATACATACGCACTAAAGCAAAGATAACATAATTTATAAATTATGA
GGTACAGAATAGTTAGATTCTGAAAATTAAAATAATCAGGAAAAACTTCATGAAGATGAGATCTGGGCT
GGATCCCAAAGGATAGGCAGGTGGATCATGTAGAACAGGGGAAAGGAGTTCCTGATCGGGGA

SNP13B_Y1323898 (R=G/A) (SEQ ID NO: 520)
GAAACTAAAGAAAGCCACAAAAGTTCACCTCAATGCCAAGACATTTCTTGATTTTTGAAAACCCAGTTG
TCGAACCACCCATCTATAGAAACTTGAAAGACTAAAAACTATCTTACTCTAAACATTTTCTAGGAAGTT
GATTCTACAACACATTTTGGTTTTCCAATTTGGCTTCTAATAATTATTTCAAAGTTTCTGTG
R
CCTAAATTTTGTTTTACATTGATCCTTTGAATGGACTACTGTTTCCACATTTTAGAACATTTAAAAAGA
TATCTACAACCCGAGTCTAATCATAAAAAAAATCAGACAGATCCAAAATGTGGAACATTCCACTAAAAA
AGGAGTGGGGAGAGGTCTTTATTCTTCCAAAAATATCAATGCCATAAAAGACAAAGACGGCT

SNP13B_K912392 (Y=T/C) (SEQ ID NO: 521)
TGTGGTATGAGGTAAGGATCCATTTTTTTCCCATTTGCATAGCCAGTTTTTGTAGCTCCACTTTATTTT
CTCACTTGATCTGCCATGCCACCTCTAGCATGTATCAACATATCATGTATGTGTGCAGCTGTTCCTTAA
CTCTCAATTTTATTCTCTTGGTTACTTTGTCTAACCCAGCACTCATACTTTTTAAATTATTA
Y
GGCTACCTTGTAGGGCAAGAATCCTCACTTTTATTCAACTTCTTTTGAAGTGTCTTGATGCATATTTTT
TCTGATCTTACTTGGCCATATATATTTTGGGGACAGATGTGACATCATACCAAGCTTTCTTTGCTTGAC
ATTGTAGATATTTTCTTATTCATTAATGTGCTAAAAATTTTGAGTTTGGTCATACAGTCTTT

SNP13B_R1556428 / DG00AAFQR (R=G/A) (SEQ ID NO: 522)
GAGATTATATCCCACCTACCACTGCAGCTCCAGGATCCAGCTTCACAAACATTTGTTGAATGAATGAAT
AAGAAAAGAGGACACCCCCAAAGAGGCTGCAAGGGAAAAAGCTACAAAGACAGAAGCACCAGGAAAAAG
TAGGGTCATGTAAGTCAAAGCAGGAAAAAAGTTCCATGGTGGGGTGGTCAGCAGTGTCTAAT
R
CCACGAAGGCACAAAGTAGGATAAAGGTTAAAAATCAGCCTTTGGTTTTGGCAAATATGAAGCTTATCG
GTAGCCTTAGCGAGAACAATTCCATCAGGGAGCAGAAGCTAACTGCAGTGGGTTGAGTCATCAAGCAGG
CATAAGGAAGTAGGGATACCCCATTATAAGCTACTCTTTCAAGAAGCTCAAATCTGAAGGTT

DG00AAFIV (W=T/A) (SEQ ID NO: 523)
TATAAATGATCATTATGTTCATATTCACACATACAATAATGTACTCAAGTTTATTGCTAAGGTAATTCA
GAATCTCCTTATTTTGAAGTGTGCATTTGATATACCTGTTTGGGAATAACTAGTTTCTTATCTTTGACA
GAAAATAATTTTGTTGTTTTGTTTTTACTAAAAAAGCATGGTGAAAAATGGCTCCATTTCTA
W
GAGAGGTAACTAAAATATCGCAATTTGCTGGGTGTCATTAAAGTAACTCACAAGGGAAAAAATGCAAAT
TGGTATCTGCTGATGGAGTAAATCTCCGCAGAAGTGATGACCCTGAAAGGATCAATATATTAAAGCCCC
TCCCAGCTGGTCATTCCAGATTGCAACAATAAAGCATTAAGTGTTAAAACCTCAAGGCAGCT

DG00AAFJT (M=C/A) (SEQ ID NO: 524)
ATCTTCAGAAATTGTAATGATGAAAGAGTGCAAGCTCTCACTTCCCCTTCCTGTACAGGGCAGGTTGTG
CAGCTGGAGGCAGAGCAGTCCTCTCTGGGGAGCCTGAAGCAAACATGGATCAAGAAACTGTAGGCAATG
TTGTCCTGTTGGCCATCGTCACCCTCATCAGCGTGGTCCAGAATGGTAAGGAAAGCCCTTCA
M

FIG. 7 T

TCAGGGAAGAACAGAAGGGGAGATTTTCTTTGATGGTTGTTTGGAAGTCAGGCTTAAACAATTGTGTCT
GTGTGTGCGCATGCACAAACACTTTTACCTTATCTTTATTTTCTTCTTTTTATTTGAATGTATAGGGTT
GTGTGTATTTCTGTGTAAATTTGGGGTTTTCCTCCTCTTAGTCTTTCACTTTTGTGGTGATT

DG00AAHII (R=G/A) (SEQ ID NO: 525)
AATTTTGGAAGCATTTTTCATATGCAGTGTATACTTCAGAAAGAGAGAGAGAGAGAGGAAAATTGTCCT
GTTCAGCGTTTGCATTTCCATTATTCCTGCTATTAGTTAAAAACAACAACAACAACAAAAAACAAGCAG
GATACCTAGATCTGGAAAAGGGAGAATTGTGTAGAGCTGTCTTCCTAAAGTTCTGAGTTAGG
R
CTGCCTCAGACCACTTTCATAACTATCTCCAGTGGCTTTGTGTTTTATATTTATTAAGATAGAGAAAAA
AAGAGTAATTACTAAGGGCAGCTGCTGTAGCTTTATGGTGATTACTGAACATTGACATGCTGTCACGTT
TTTGGAACTTTGAGTATTTAATCACTTTGGGATATTCTATTTTCCCCCATCTTGAGTGTGGA

DG00AAHID (W=T/A) (SEQ ID NO: 526)
ACAGTTGTCCTGCCTGTGTTCAGGAAGGGAGTTTCTGTGGTCCCTTTGAAACCACAGAAGAGCCCCTCG
TATAGCTCTCAATGGAGGGGGCAAAACATTCAAATAACTCAGGAGATAACACAACTATTTGTTTTTAAC
TGTGAGTTTTTAGGCAATCACAAAGATCCAGATGTATGTCCAAGCCTCTCTTTGCAATTCTA
W
TTAACCTCAATGTTGCAACCATAGACCTACCTTACAGAGTTCAAAAAAATATGCAAAAACCCTGCCTTT
CTTCTTCCTCATACCCCAAAATGCCATTCTGAACATTTCCTGTTAGTTAAAAAAAGATTTCCATGGTGT
TACCAGGCACTGTACACAGTCTGTGTCCCAAGACAAGGAGGTACAGTTCCACATGCGCCCAT

DG00AAHIJ (R=G/A) (SEQ ID NO: 527)
AATCATCTGACTTTAGAGAGTAGACACTTGCTCCATGCATATTGCCTCCAATTCATTCATTCAAGCACT
CCCTGCTCAAGAAGTTCTTTCTTATGTTGAGCTGAAATCTGCAGCCCTATGCGTTTTACCCAGCAGTCC
TGGTGCTGTTCCCTAAAATCACTTAGACTGTGCCTGCTCTTTCTGTGTTTACAGTGTCAGCT
R
TAATATCCCCCTCTTCGGCCTAACGTTTCTGAAGTCCCTTGCCACTGGGTCTCCTCTCCTCTTCCTGTG
TTCTTTCTAAGAACACCTATGCAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCTGAGATCCGGGCAT
CGACTCTGTTAGAATAATCTACGTATGAGTTATTTTTTTGAGAACTATGTGTCATTGCTGAC

DG00AAHIH (R=G/A) (SEQ ID NO: 528)
TTATGTTGAGCTGAAATCTGCAGCCCTATGCGTTTTACCCAGCAGTCCTGGTGCTGTTCCCTAAAATCA
CTTAGACTGTGCCTGCTCTTTCTGTGTTTACAGTGTCAGCTGTAATATCCCCCTCTTCGGCCTAACGTT
TCTGAAGTCCCTTGCCACTGGGTCTCCTCTCCTCTTCCTGTGTTCTTTCTAAGAACACCTAT
R
CAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCTGAGATCCGGGCATCGACTCTGTTAGAATAATCTA
CGTATGAGTTATTTTTTTGAGAACTATGTGTCATTGCTGACTCATATTAACTCTGTGGTTAACTAAAAT
CTCAAGATCTCTTTATGTTTGTTGAGAAACTTATTTAACTTCTCTGGCCCTCCGTTTCCTTC

DG00AAHIE (M=C/A) (SEQ ID NO: 529)
AACACCTATGCAGATAGGTGTCTTCTGTACAGGGAAGCTGTTCCTGAGATCCGGGCATCGACTCTGTTA
GAATAATCTACGTATGAGTTATTTTTTTGAGAACTATGTGTCATTGCTGACTCATATTAACTCTGTGGT
TAACTAAAATCTCAAGATCTCTTTATGTTTGTTGAGAAACTTATTTAACTTCTCTGGCCCTC
M
GTTTCCTTCACTGAGCAGTGGAGTGATTGATAACCTCCACCTGTGGTTGCTGAAGGTCTTGCACAAGAT
GATATAGTTAAAGTAGCTAGCAGTGCCCACGTACGGCGGATGCCTCACAACGGTTTGCAGCCATCTCTC
TATCTGTGTCTTTGTCTCTCTCTCACACTGGTTTTGGCTTACTGTTAGCAGCTAGCCGAGAT

DG00AAHIG (Y=C/T) (SEQ ID NO: 530)
CAAAGAAGGTGTCTTTGATGAGGCAAGGTCAAAACTTCTCCCCAGACGAAATCCAAAGAAAGCATTCCT
ACTATGCTATATCAGTTTGGAAAGAAAAACTTCTGCCAGGTGACTGCATTCTCACTGGTCACATTGTGT
TCCTATGGACTCCTCAGCTCAACCAATTTGGAGAAGTTATGGTGCAATTTCACCATATCTGG
Y
TAGAAGTTAAGTTTCCAATTTGCTGGCAATGAAGAAGAAATGGAGCAGGCCAGGCTGTGTAGTTTCTGC
CACGTGCCCCCGGGAGTGAACAGCTCTGTTTGTAAGAAGCCATGGTGCTTAGACCTGGGCTCGCTAGTT
GCCAGCCTCCAAATTGCAGAAGTGCCCTTTGGTTGGTGGCTATGCTGTGTCACTTGGGAAGG

DG00AAHIF (S=G/C) (SEQ ID NO: 531)

FIG. 7U

CCTGGGAAAACTAAAGTAAATCAGACACCCGACGTGTGAGCTAGGTTATAATATGCCCAGTGGACCCTG
GGGACATCTTAGCTTTCAGAGGTCATGCTGTCCAAGCTGACTGTGGGGCTTCCAGAAGGTGGGGAGAGG
AAATGATGCAATGGCCCATCAGAGGCACTACTTGGGGCCTGGGGCCAGAGTGCATGTCTAAG
S
CATTAAGGGGAGGGGAGAGCAGCCTTCATAATTATGAAGAGGAGTCTCAGGTGCACAGCTTCTGATGAG
GGACAGCTTCTAATTGAAGACAGCATTGTGTAATGCTCAAACTCCCTGTCTTCAGAGTGCCTGCTGTAT
CCCACCATCAGTTCTGTGACTTCTCCCTAAGCCTCAATTTTGCATGTGTTACATTGGGATAA

DG00AAHOI (R=G/A) (SEQ ID NO: 532)
GGAGAACATGATTAGCATATTTTTTTTAAGTGAACTTTAGACCCTTTTTTAAAGGCCTATCTGATTAGG
CCAGGCCCAAGTGAGCTTTAAGTCAACTGATTAGAGATCTTAATTACATCTGCAAAGTCCCTTCATGTT
TACCGTATAACATAACTTAGTGAAAGGAGTGAAATTGCAACCAGGTTCTGCCTGCACTCCAC
R
GAAGGGGATTCTGCAGAAGTGTGGGTCACGGGGGGGTTATTTTGGGATTCTGCCTACGTCACTGAGTCA
AAAGAAGCTGAATGGTTGTGATGCTGAGGTTTTTGGGCAGCAGCAGTGTGTGTGTGTGAGTGAATTCAT
ACGTATGACCACCTGGGAAGAAAGGAGGCTGTGGTTTCCTCCACCTCCTGGCAGACAGAGAA

SG13S35 / FLA324333 (R = G/A) (SEQ ID NO: 533)
AGTGCTCTCTAAAGAGCAGTGCTCTACCATCCAAGCTGGGCTTTTCTTTTCTTCTTGCTGATAGGGAAG
GCATGGGACATTGCAGGATGGAAGTGGCCCCCAGGCCTTCTCATGCCTGGGCTTGGTTTGGAAGGTGGT
CAGGTGATCAATAATCCTGATTGGCCTGGCATTGAGGAGTTTTCCTGGGATGTGGTCCTTTC
R
GTTTTTTAAAAATTATTTTTATTGATACACATATTTGTAGGTATTTGTGGGGTGCATGTGATACTTTAT
TATGTGTGTGGATTGTGTAATGATGAAGTCAGGGCATTTAGGGTCTTCATCACCTTGATTATCATTTCT
ATGTGTTGAGAACATTTCAAGTTCTCAGTTCCAGCTATTTTGAAATAGACAGTCCATTTTGT

DG00AAFIU / SNP_13_Y1323892 (Y=C/T) (SEQ ID NO: 534)
CTTCTTTTGCCCTGCCTTTCTGCCTTTCTGTCCTTTTAATTTGCGGGCTTTTGGCAACCACAGCACGGG
TCTGGTTTCCTAGGAGTTTCTTTTGTAGGATCAAACCGCTAGTTGGCTCTTGGCCCTGTGATAGGGCCC
TGGGCTAACTTATTGGGAAAATGTTGCTGTAACCCCTGCCCAGAGGTGCCTGTGACATGGGC
Y
GCCATCTTCTCCTCTTCCCTTGGCTTCAGCCCCACCTAGAAACCTGAACAAACATTTTCCTTGACATTT
CATAAAGTGTCAGTGGCTCCTCATTTAGCAAAATACATCCCAGGGAAGTTCAAAAGTGAAAAAAGGCCG
TAACTTCTTCTTCTTCTCAGGGACCTACAGAAAATATGTGGCACCTCGGCAGCCTGGCCTGC

DG00AAJFF / FLA287889 (R = G/A) (SEQ ID NO: 535)
GTGCAGTGGCGTGATCCCAGCTCACTGCAATCTCTGCCTCCTGGGTTCAAGTGATTCTCCTGCCTCAGC
CTCCCGAGGGGCTGGGATTGTAGGCGTGCACCACTATGCCCATCTAATTTTTGTATTTTTAGTAGAGAT
AGGGTTTTGCCATTTTGGCCAGACTGTCTTGAACTCCTGACCTCAGGTGATCTGCCTGCCTC
R
GCCTCCCACAGTTTTGTGATTATAGGCATGAGCCACCGTGCCCGGCCTTAACCTTTGTTTTCTTACACA
ACACACTACGTGATGTTTTCCACATGCATGGGTCATTTGCTTCATTTACGTACAAATGCATAAGCAATA
TACTGTGTGGTGTGAGTTTGTGATGGGAAAAGGAAGAAGTTTTGCGGATACTACACTGGCTT

FIG. 7v